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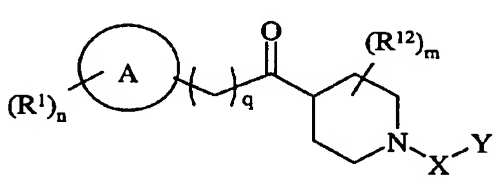
(54) Title: 1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES AND THEIR USE AS 11-BETAHSD1 INHIBITORS



(I)

(57) Abstract: The use of a compound of formula (I) in the manufacture of a medicament for use in the inhibition of 11βHSD1 is described.

1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES AND THEIR USE AS 11-BETAHSD1 INHIBITORS

This invention relates to chemical compounds, or pharmaceutically acceptable salts thereof. These compounds possess human 11-β-hydroxysteroid dehydrogenase type 1 enzyme (11βHSD1) inhibitory activity and accordingly have value in the treatment of disease states including metabolic syndrome and are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit 11βHSD1in a warm-blooded animal, such as man.

Glucocorticoids (cortisol in man, corticosterone in rodents) are counter regulatory hormones i.e. they oppose the actions of insulin (Dallman MF, Strack AM, Akana SF et al. 1993; Front Neuroendocrinol 14, 303-347). They regulate the expression of hepatic enzymes involved in gluconeogenesis and increase substrate supply by releasing glycerol from adipose tissue (increased lipolysis) and amino acids from muscle (decreased protein synthesis and increased protein degradation). Glucocorticoids are also important in the differentiation of pre-adipocytes into mature adipocytes which are able to store triglycerides (Bujalska IJ et al. 1999; Endocrinology 140, 3188-3196). This may be critical in disease states where glucocorticoids induced by "stress" are associated with central obesity which itself is a strong risk factor for type 2 diabetes, hypertension and cardiovascular disease (Bjorntorp P & Rosmond R 2000; Int. J. Obesity 24, S80-S85)

It is now well established that glucocorticoid activity is controlled not simply by secretion of cortisol but also at the tissue level by intracellular interconversion of active cortisol and inactive cortisone by the 11-beta hydroxysteroid dehydrogenases, 11βHSD1 (which activates cortisone) and 11βHSD2 (which inactivates cortisol) (Sandeep TC & Walker BR 2001 Trends in Endocrinol & Metab. 12, 446-453). That this mechanism may be important in man was initially shown using carbenoxolone (an anti-ulcer drug which inhibits both 11βHSD1 and 2) treatment which (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159) leads to increased insulin sensitivity indicating that 11βHSD1 may well be regulating the effects of insulin by decreasing tissue levels of active glucocorticoids (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159).

Clinically, Cushing's syndrome is associated with cortisol excess which in turn is associated with glucose intolerance, central obesity (caused by stimulation of pre-adipocyte differentiation in this depot), dyslipidaemia and hypertension. Cushing's syndrome shows a

number of clear parallels with metabolic syndrome. Even though the metabolic syndrome is not generally associated with excess circulating cortisol levels (Jessop DS et al. 2001; J. Clin. Endocrinol. Metab. 86, 4109-4114) abnormally high 11βHSD1 activity within tissues would be expected to have the same effect. In obese men it was shown that despite having similar or lower plasma cortisol levels than lean controls, 11βHSD1 activity in subcutaneous fat was greatly enhanced (Rask E et al. 2001; J. Clin. Endocrinol. Metab. 1418-1421). Furthermore, the central fat, associated with the metabolic syndrome expresses much higher levels of 11βHSD1 activity than subcutaneous fat (Bujalska IJ et al. 1997; Lancet 349, 1210-1213). Thus there appears to be a link between glucocorticoids, 11βHSD1 and the metabolic syndrome.

11βHSD1 knock-out mice show attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting and lower plasma glucose levels in response to stress or obesity (Kotelevtsev Y et al. 1997; Proc. Natl. Acad. Sci USA 94, 14924-14929) indicating the utility of inhibition of 11βHSD1 in lowering of plasma glucose and hepatic glucose output in type 2 diabetes. Furthermore, these mice express an anti-atherogenic lipoprotein profile, having low triglycerides, increased HDL cholesterol and increased apo-lipoprotein AI levels. (Morton NM et al. 2001; J. Biol. Chem. 276, 41293-41300). This phenotype is due to an increased hepatic expression of enzymes of fat catabolism and PPARα. Again this indicates the utility of 11βHSD1 inhibition in treatment of the dyslipidaemia of the metabolic syndrome.

The most convincing demonstration of a link between the metabolic syndrome and 11βHSD1 comes from recent studies of transgenic mice over-expressing 11βHSD1 (Masuzaki H et al. 2001; Science 294, 2166-2170). When expressed under the control of an adipose specific promoter, 11βHSD1 transgenic mice have high adipose levels of corticosterone, central obesity, insulin resistant diabetes, hyperlipidaemia and hyperphagia. Most importantly, the increased levels of 11βHSD1 activity in the fat of these mice are similar to those seen in obese subjects. Hepatic 11βHSD1 activity and plasma corticosterone levels were normal, however, hepatic portal vein levels of corticosterone were increased 3 fold and it is thought that this is the cause of the metabolic effects in liver.

Overall it is now clear that the complete metabolic syndrome can be mimicked in mice simply by overexpressing 11βHSD1 in fat alone at levels similar to those in obese man.

11βHSD1 tissue distribution is widespread and overlapping with that of the glucocorticoid receptor. Thus, 11βHSD1 inhibition could potentially oppose the effects of glucocorticoids in a number of physiological/pathological roles. 11βHSD1 is present in human skeletal muscle and glucocorticoid opposition to the anabolic effects of insulin on protein turnover and glucose metabolism are well documented (Whorwood CB et al. 2001; J. Clin. Endocrinol. Metab. 86, 2296-2308). Skeletal muscle must therefore be an important target for 11βHSD1 based therapy.

Glucocorticoids also decrease insulin secretion and this could exacerbate the effects of glucocorticoid induced insulin resistance. Pancreatic islets express 11βHSD1 and carbenoxolone can inhibit the effects of 11-dehydocorticosterone on insulin release (Davani B et al. 2000; J. Biol. Chem. 275, 34841-34844). Thus in treatment of diabetes 11βHSD1 inhibitors may not only act at the tissue level on insulin resistance but also increase insulin secretion itself.

Skeletal development and bone function is also regulated by glucocorticoid action. 11βHSD1 is present in human bone osteoclasts and osteoblasts and treatment of healthy volunteers with carbenoxolone showed a decrease in bone resorption markers with no change in bone formation markers (Cooper MS et al 2000; Bone 27, 375-381). Inhibition of 11βHSD1 activity in bone could be used as a protective mechanism in treatment of osteoporosis.

Glucocorticoids may also be involved in diseases of the eye such as glaucoma. 11βHSD1 has been shown to affect intraocular pressure in man and inhibition of 11βHSD1 may be expected to alleviate the increased intraocular pressure associated with glaucoma (Rauz S et al. 2001; Investigative Opthalmology & Visual Science 42, 2037-2042).

There appears to be a convincing link between 11βHSD1 and the metabolic syndrome both in rodents and in humans. Evidence suggests that a drug which specifically inhibits 11βHSD1 in type 2 obese diabetic patients will lower blood glucose by reducing hepatic gluconeogenesis, reduce central obesity, improve the atherogenic lipoprotein phenotype, lower blood pressure and reduce insulin resistance. Insulin effects in muscle will be enhanced and insulin secretion from the beta cells of the islet may also be increased.

Currently there are two main recognised definitions of metabolic syndrome.

1) The Adult Treatment Panel (ATP III 2001 JMA) definition of metabolic syndrome indicates that it is present if the patient has three or more of the following symptoms:

- Waist measuring at least 40 inches (102 cm) for men, 35 inches (88 cm) for women;

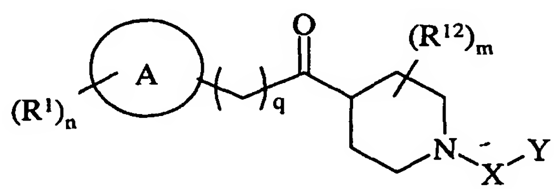
- Serum triglyceride levels of at least 150 mg/dl (1.69 mmol/l);
- HDL cholesterol levels of less than 40 mg/dl (1.04 mmol/l) in men, less than 50 mg/dl (1.29 mmol/l) in women;
- Blood pressure of at least 135/80 mm Hg; and / or
- Blood sugar (serum glucose) of at least 110 mg/dl (6.1 mmol/l).

2) The WHO consultation has recommended the following definition which does not imply causal relationships and is suggested as a working definition to be improved upon in due course:

- The patient has at least one of the following conditions: glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus and/or insulin resistance; together with two or more of the following:
- Raised Arterial Pressure;
- Raised plasma triglycerides
- Central Obesity
- Microalbuminuria

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective 11βHSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

Accordingly there is provided the use of a compound of formula **(I)**:



(I)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl,

N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -$S(O)_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O-, -C(=NR^{11})- or -CH_2-; wherein $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-4}alkyl, carbocyclyl and heterocyclyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-N-(C_{1-4}alkyl)amino, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, N-(C_{1-4}alkyl)aminothiocarbonylthio, N,N-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-N-(C_{1-4}alkyl)amino, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8; and wherein if said

heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^4, R^5, R^7 R^9 and R^{13} are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein a is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is hydroxy, methyl, ethyl or propyl;

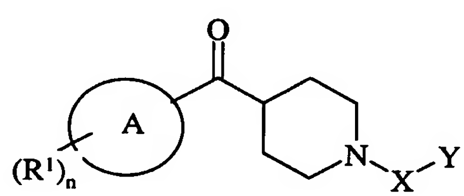
m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

Accordingly to another feature of the invention, there is provided the use of a compound of formula **(I')**:



(I')

wherein:

Ring A is selected from aryl or heteroaryl; wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino,

C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Y- and heterocyclylC_{0-4}alkylene-Y-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

X is -C(O)-, -S(O)$_2$- or -CH$_2$-;

Y is C_{1-6}alkyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Y- and heterocyclylC_{0-4}alkylene-Y-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

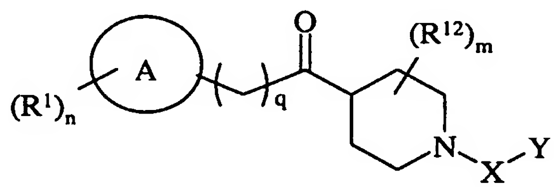
$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^7}$ and $\mathbf{R^9}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

Accordingly there is provided the use of a compound of formula **(I")**:



(I")

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein **R^{11}** is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^7}$ and $\mathbf{R^9}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^8}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl,

N-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C$_{1-4}$alkyl;

R^{12} is methyl or ethyl;

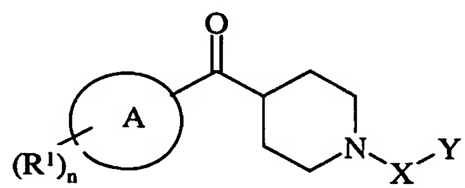
m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

In a further aspect of the invention, there is provided a compound of formula **(Ia)** wherein:



(Ia)

wherein:

Ring A is thienyl, furyl or thiazolyl;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C$_{1-4}$alkyl, C$_{2-4}$alkenyl, C$_{2-4}$alkynyl, C$_{1-4}$alkoxy, C$_{1-4}$alkanoyl, C$_{1-4}$alkanoyloxy, *N*-(C$_{1-4}$alkyl)amino, *N,N*-(C$_{1-4}$alkyl)$_2$amino, C$_{1-4}$alkanoylamino, *N*-(C$_{1-4}$alkyl)carbamoyl, *N,N*-(C$_{1-4}$alkyl)$_2$carbamoyl, C$_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, C$_{1-4}$alkoxycarbonyl, *N*-(C$_{1-4}$alkyl)sulphamoyl, *N,N*-(C$_{1-4}$alkyl)$_2$sulphamoyl, C$_{1-4}$alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC$_{0-4}$alkylene-Z- and heterocyclylC$_{0-4}$alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC$_{1-4}$alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

X is -C(O)- or -S(O)$_2$-;

Y is C$_{1-6}$alkyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

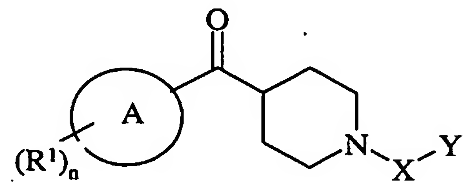
R^4, **R^5** and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;
or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not
1-acetyl-4-[(4-methylthien-2-yl)carbonyl]piperidine;
1-acetyl-4-[(4-methyl-5-bromothien-2-yl)carbonyl]piperidine; or
1-benzoyl-4-[(5-methylthien-2-yl)carbonyl]piperidine.

In a further aspect of the invention, there is provided a compound of formula **(Ib)** wherein:



(Ib)

wherein:

Ring A is pyridinyl;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

X is -C(O)- or -S(O)$_2$-;

Y is C_{1-6}alkyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl,

N-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

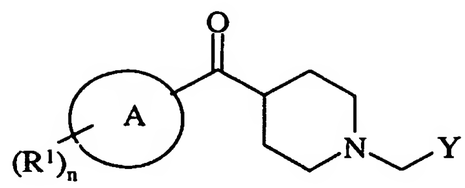
R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, **R^5** and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;
or a pharmaceutically acceptable salt thereof;
with the proviso that said compound is not
1-(piperidin-4-ylcarbonyl)-4-(pyridin-2-ylcarbonyl)piperidine.

In a further aspect of the invention, there is provided a compound of formula **(Ic)**:



(Ic)

wherein:

Ring A is selected from thienyl, furyl, thiazolyl or pyridyl;

R[1] is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is phenyl, pyridyl, thienyl, furyl or thiazolyl; wherein Y may be optionally substituted on carbon by one or more R^2;

R[2] is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R[3] and **R**[6] are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl,

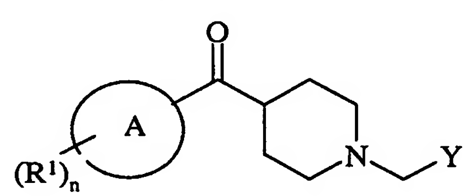
N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4 and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;
or a pharmaceutically acceptable salt thereof;
with the proviso that said compound is not
1-(2-hydroxypyrid-3-ylmethyl)-4-(thien-2-ylcarbonyl)piperidine;
1-(2-methoxypyrid-3-ylmethyl)-4-(thien-2-ylcarbonyl)piperidine or
1-benzyl-4-(thien-2-ylcarbonyl)piperidine.

In a further feature of the invention, there is provided a compound of formula **(Id)**:



(Id)

wherein:

Ring A is phenyl;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino,

C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; or two R^1 on adjacent carbons may form an oxyC_{1-4}alkoxy group; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is thienyl, furyl or thiazolyl; wherein Y may be optionally substituted on carbon by one or more R^2;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

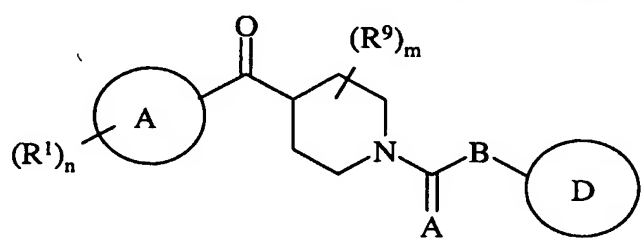
$\mathbf{R^8}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl,

acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is $-S(O)_a-$, -O-, $-NR^{10}-$, -C(O)-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-OC(O)NR^{10}-$ or $-SO_2NR^{10}-$; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl; or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not
1-(thien-2-ylmethyl)-4-(4-mesylaminobenzoyl)piperidine or
1-(5-methylfur-2-ylmethyl)-4-(4-mesylaminobenzoyl)piperidine.

In a further aspect of the invention there is provided a compound of formula **(Ie)**:



(Ie)

wherein:

Ring A is selected from carbon linked pyridyl, thienyl, furyl and thiazolyl;

A is O or S;

B is O or N;

Ring D is carbocyclyl or heterocyclyl; wherein Ring D may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally

substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, $-S(O)_2-$, $-C(O)NR^{11}-$, $-C(S)NR^{11}-$, -C(O)O- or $-CH_2-$; wherein $\mathbf{R^{11}}$ is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-$(C_{1-4}alkyl)_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-$(C_{1-4}alkyl)_2$carbamoyl, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-$(C_{1-4}alkyl)_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-$(C_{1-4}alkyl)_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-$(C_{1-4}alkyl)_2$carbamoyl, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-$(C_{1-4}alkyl)_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

$\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^7}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-$(C_{1-4}alkyl)_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R⁸ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is $-S(O)_a-$, -O-, $-NR^{10}-$, -C(O)-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-OC(O)NR^{10}-$ or $-SO_2NR^{10}-$; wherein **a** is 0 to 2; wherein $\mathbf{R^{10}}$ is selected from hydrogen and C_{1-4}alkyl;

$\mathbf{R^{12}}$ is methyl or ethyl;

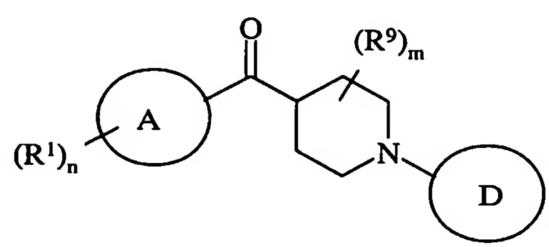
m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not 1-(2-cyano-4,5-dimethoxyanilinothiocarbonyl)-4-(thien-2-ylcarbonyl)piperidine.

In a further aspect of the invention there is provided a compound of formula **(If)**:



(If)

wherein:

Ring A is selected from carbon linked pyridyl, thienyl, furyl and thiazolyl;

Ring D is carbon linked phenyl, pyridyl, thienyl, furyl and thiazolyl; wherein Ring D may be optionally substituted on carbon by one or more R^2; wherein said thiazolyl may be optionally substituted on nitrogen by a group selected from R^5;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl,

carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein $\mathbf{R^{11}}$ is selected from hydrogen and C_{1-4}alkyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^4, **R^5** and **R^7** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

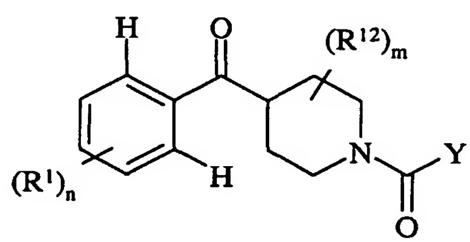
R^{12} is methyl or ethyl;

m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention there is provided a compound of formula **(Ig)**:



(Ig)

wherein:

R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylS(O)$_2$, *N*-(C_{1-4}alkyl)sulphamoyl or *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is phenyl, pyrimidine, furan, thiophene or thiazole; wherein Y may be optionally substituted on carbon by one or more R^2;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, *N*-(C_{1-4}alkyl)aminothiocarbonylthio or *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl or C_{1-4}alkylsulphonylamino; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not 1,4-dibenzoylpiperidine; 4-hydroxy-1,4-dibenzoylpiperidine; 1-(3,4,5-trimethoxybenzoyl)-1-benzoylpiperidine; 1,4-di-(4-methylbenzoyl)piperidine; 1-(4-chlorobenzoyl)-4-benzoylpiperidine;

1-(3-nitrobenzoyl)-4-benzoylpiperidine;

1-(2-methoxy-4,6-ditrifluoromethylbenzoyl)-4-(4-chlorobenzoyl)piperidine;

1-(2,6-difluorobenzoyl)-4-benzoylpiperidine;

1-(3-trifluoromethylbenzoyl)-4-(benzoyl)piperidine;

1-(4-aminobenzoyl)-4-(4-fluorobenzoyl)piperidine;

1-(2-chloro-4-nitrobenzoyl)-4-benzoylpiperidine; 1-(4-methoxybenzoyl)-4-benzoylpiperidine;

1-(4-*t*-butylbenzoyl)-4-benzoylpiperidine;

1-(2,4-dihydroxybenzoyl)-4-(4-fluorobenzoyl)piperidine;

1-(4-nitrobenzoyl)-4-(4-fluorobenzoyl)piperidine;

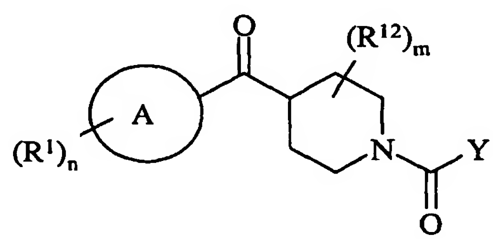
1-(pyrid-3-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;

1-(thien-2-ylcarbonyl)-4-benzoylpiperidine;

1-(thien-2-ylcarbonyl)-4-(4-methylbenzoyl)piperidine; or

1-(fur-2-ylcarbonyl)-4-benzoylpiperidine.

According to a further aspect of the invention there is provided the use of a compound of formula **(Ih)**:



(Ih)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said

heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, *N*-(C_{1-4}alkyl)aminothiocarbonylthio, *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

$\mathbf{R^3}$ and $\mathbf{R^6}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^7}$ $\mathbf{R^9}$ and R^{13} are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is $-S(O)_a-$, -O-, $-NR^{10}-$, -C(O)-, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, $-OC(O)NR^{10}-$ or $-SO_2NR^{10}-$; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

For the avoidance of doubt, where X is $-C(O)NR^{11}-$, $-C(S)NR^{11}-$ or -C(O)O- is it the C(O) or the C(S) that is attached to the nitrogen of the piperidine ring in formula **(I)**.

Also for the avoidance of doubt, where the use etc of compounds of formula **(I)** is referred to herein, it is to be understood that this also refers to the use of compounds of formula **(I')** and **(I'')** as well.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" includes propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals therefore "carbocyclylC_{1-4}alkyl" would include 1-carbocyclylpropyl, 2-carbocyclylethyl and 3-carbocyclylbutyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless

otherwise specified, be carbon or nitrogen linked. Suitably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8 - 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, furyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, benzothienyl, pyridyl and quinolyl. Particularly "heteroaryl" refers to thienyl, furyl, thiazolyl, pyridyl, benzothienyl, imidazolyl or pyrazolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Suitably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono, bicyclic or tricyclic ring containing 3-15 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a -C(S)-, or a ring sulphur atom may be optionally oxidised to form the S-oxides. Particularly a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a -C(S)-, or a ring sulphur atom may be optionally oxidised to form the S-oxides. More particularly a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thienyl, piperidinyl, morpholinyl, furyl, thiazolyl, pyridyl, imidazolyl, 1,2,4-triazolyl, thiomorpholinyl, coumarinyl, pyrimidinyl, phthalidyl, pyrazolyl, pyrazinyl, pyridazinyl, benzothienyl, benzimidazolyl, tetrahydrofuryl, [1,2,4]triazolo[4,3-a]pyrimidinyl, piperidinyl, indolyl, 1,3-benzodioxolyl and

pyrrolidinyl. Further examples and suitable values of the term "heterocyclyl" are 1,3-benzodioxolyl, thienyl, furyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2*H*-indazolyl, imidazo[2,1-*b*][1,3]thiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, 2,3-dihydro-1-benzofuryl, 2,3-dihydro-1,4-benzodioxinyl and pyridyl. Further examples and suitable values for the term "heterocyclyl" are benzofuranyl, 2,1-benzisoxazolyl, 1,3-benzodioxolyl, 1,3-benzothiazolyl, benzothienyl, 3,4-dihydro-2H-benzodioxepinyl, 2,3-dihydro-1,4-benzodioxinyl, chromanyl, 2,3-dihydrobenzofuranyl, furyl, imidazo[2,1-b][1,3]thiazolyl, indolyl, isoindolinyl, isoquinolinyl, isoxazolyl, morpholinyl, oxazolyl, piperidinyl, pyrazinyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, 4,5,6,7-tetrahydro-1-benzofuryl, 4,5,6,7-tetrahydro-2H-indazolyl, 4,5,6,7-tetrahydro-1H-indolyl, tetrahydropyranyl, 1,2,3,4-tetrahydroquinolinyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl or thienyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono, bicyclic or tricyclic carbon ring that contains 3-15 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Particularly a "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclohexyl, phenyl, naphthyl or 2-6-dioxocyclohexyl. More particularly "carbocyclyl" is phenyl, naphthyl, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl or indenyl. More particularly "carbocyclyl" is naphthyl, phenyl, cyclopropyl, cyclohexyl, indenyl, 1,2,3,4-tetrahydronaphthyl, cyclopentyl or (3r)-adamantanyl.

An example of "C_{1-4}alkanoyloxy" is acetoxy. Examples of "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-4}alkoxy" include methoxy, ethoxy and propoxy. Examples of "oxyC_{1-4}alkoxy" include oxymethoxy, oxyethoxy and oxypropoxy. Examples of "C_{1-4}alkanoylamino" include formamido, acetamido and propionylamino. Examples of and "C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and

ethylsulphonyl. Examples of and "C_{1-4}alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C_{1-4}alkanoyl" include propionyl and acetyl. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-4}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-4}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-4}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-4}alkylsulphonylamino" are mesylamino and ethylsulphonylamino. Examples of "C_{0-4}alkylene" are a direct bond, methylene and ethylene.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess 11βHSD1 inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess 11βHSD1 inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess 11βHSD1 inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Ring A is aryl.

Ring A is heteroaryl; wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is aryl or heteroaryl; wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is carbocyclyl.

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is phenyl.

Ring A is selected from phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl or furyl.

Ring A is phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl, furyl, thiazolyl, 1,3-benzothiazolyl, benzofuryl or benzothienyl.

Ring A is selected from phenyl, 1,3-benzodioxol-5-yl, thien-2-yl, cyclopentyl, pyrid-2-yl or fur-2-yl.

Ring A is phenyl wherein the positions ortho to the $(CH_2)_q$ group are unsubstituted or substituted by fluoro, preferably unsubstituted.

R^1 is selected from halo or C_{1-4}alkyl.

R^1 is a substituent on carbon and is selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein R^3 is halo; and Z is $-S(O)_a-$; wherein a is 2.

R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, *N,N*-$(C_{1-4}alkyl)_2$amino, $C_{1-4}alkylS(O)_a$ wherein a is 0 to 2, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein

R^3 is selected from halo, hydroxy, C_{1-4}alkoxy, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; and

Z is $-S(O)_a-$ or -O-; wherein a is 0 to 2.

R^1 is selected from fluoro, chloro or methyl.

R^1 is selected from fluoro, chloro, methoxy or methyl.

R^1 is a substituent on carbon and is selected from fluoro, chloro, bromo, methyl, *t*-butyl, propyl, methoxy, phenyl or 6-bromonaphth-2-ylsulphonyl.

R^1 is a substituent on carbon and is selected from fluoro, chloro, bromo, cyano, methyl, propyl, *t*-butyl, methoxy, ethoxy, isopropoxy, butoxy, naphth-2-ylthio, naphth-2-ylsulphonyl, phenyl, methylthio, isopropylthio, mesyl, isopropylsulphonyl, methylsulphinyl, isopropylsulphinyl and dimethylamino; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein

R^3 is selected from fluoro, bromo, hydroxy, methoxy, benzyloxy and thienyl; and

Z is $-S(O)_a-$; wherein a is 0 to 2.

n is 0-3; wherein the values of R^1 may be the same or different.

n is 0-2; wherein the values of R^1 may be the same or different.

n is 0 or 1.

n is 2; wherein the values of R^1 may be the same or different.

n is 1.

n is 0.

Ring A is phenyl, n is 1 and the substituent is para to the carbonyl of formula (I).

Ring A, R^1 and n together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-propylphenyl, 4-*t*-butylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-(6-bromonaphth-2-ylsulphonyl)phenyl, 4-phenylphenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2-methyl-4-fluorophenyl, 2,4-dimethylphenyl, 1,3-benzodioxol-5-yl, thien-2-yl, 5-chlorothien-2-yl, cyclopentyl, pyrid-2-yl, 6-methylpyrid-2-yl and fur-2-yl.

Ring A, $(R^1)_n$ and $(CH^2)_q$ together form phenyl, 4-bromophenyl, 3-butoxyphenyl, 4-*t*-butylphenyl, 3-chlorophenyl, 4-chlorophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-dimethylaminophenyl, 3-ethoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-isopropoxyphenyl, 4-isopropoxyphenyl, 4-(isopropylthio)phenyl, 4-(isopropylsulphinyl)phenyl, 4-(isopropylsulphonyl)phenyl, 3-mesylphenyl, 4-mesylphenyl, 3-(methoxymethyl)phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methylsulphinylphenyl, 4-methylsulphinylphenyl, 3-methylthiophenyl, 4-methylthiophenyl, 4-propylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethoxyphenyl,

4-trifluoromethoxyphenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,4-dichlorophenyl, 2,4-dimethylphenyl, 2-methyl-4-fluorophenyl, 3-methyl-4-chlorophenyl, 3-methyl-4-methoxyphenyl, 3-chloro-4-fluorophenyl, 3-(benzyloxymethyl)-4-chlorophenyl, 3-(hydroxymethyl)-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 3-ethoxy-4-chlorophenyl, 4-(6-bromonaphth-2-ylthio)phenyl, 4-(6-bromonaphth-2-ylsulphonyl)phenyl, benzyl, cyclopentyl, biphenyl-4-yl, 1,3-benzodioxol-5-yl, thien-2-yl, 4-chlorothien-2-yl, 5-chlorothien-2-yl, 5-methylthien-2-yl, thien-3-yl, 6-methylpyrid-2-yl, pyrid-2-yl, fur-2-yl, 5-cyanofur-2-yl, 4,5-dimethylfur-2-yl, thiazol-2-yl, 4,5-dimethylthiazol-2-yl, 1,3-benzothiazol-2-yl, benzofur-2-yl, 5-chlorobenzofur-2-yl, benzothien-2-yl, 5-chlorobenzothien-2-yl, 5-(thien-2-yl)thien-2-yl,

Ring A, R^1 and n together form 4-fluorophenyl, 4-chlorophenyl and 4-methoxyphenyl.

X is -C(O)-.

X is $-S(O)_2-$.

X is $-CH_2-$.

X is $-C(O)NR^{11}-$; wherein R^{11} is selected from hydrogen.

X is $-C(O)NR^{11}-$; wherein R^{11} is selected from C_{1-4}alkyl.

X is $-C(O)NR^{11}-$; wherein R^{11} is selected from methyl.

X is $-C(S)NR^{11}-$; wherein R^{11} is selected from hydrogen.

X is $-C(S)NR^{11}-$; wherein R^{11} is selected from C_{1-4}alkyl.

X is -C(O)O-.

X is a direct bond.

X is $-C(=NR^{11})-$; wherein R^{11} is selected from hydrogen.

X is $-C(=NR^{11})-$; wherein R^{11} is selected from C_{1-4}alkyl.

Y is C_{1-6}alkyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is carbocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5.

Y is phenyl, thienyl, methyl, furyl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is phenyl, thien-2-yl, methyl, fur-2-yl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5.

Y is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, pentyl, naphthyl, phenyl, pyridyl, thienyl, furyl, cyclopropyl, cyclohexyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, pyrazolyl, isoxazolyl, isoquinolinyl, indenyl, 1,2,3,4-tetrahydronaphthyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, morpholinyl, piperidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, isoindolinyl, tetrahydrofuryl, imidazo[2,1-b][1,3]thiazolyl, cyclopentyl, 2,3-dihydro-1,4-benzodioxinyl, tetrahydropyranyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, benzothienyl, chromanyl, 1,2,3,4-tetrahydroquinolinyl, 1,3-benzothiazolyl, 3,4-dihydro-2H-benzodioxepinyl, (3r)-adamantanyl, pyrrolidinyl, oxazolyl, 4,5,6,7-tetrahydro-1H-indolyl, quinoxalinyl or 4,5,6,7-tetrahydro-1-benzofuryl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5.

Y is 4-methylphenyl, 4-fluorophenyl, thien-2-yl, methyl, fur-2-yl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2.

R^2 is a substituent on carbon and is selected from halo or C_{1-4}alkyl.

R^2 is a substituent on carbon and is selected from fluoro or methyl.

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 or 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6.

R^6 is selected from halo, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonylamino, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl.

R^8 is selected from halo.

Z is -S(O)$_a$-, -O-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen.

When Y is phenyl, R^2 is para to X.

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 or 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonylamino, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl;

R^8 is selected from halo; and

Z is -S(O)$_a$-, -O-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen.

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, carbocyclyl, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl, C_{1-4}alkanoyl and C_{1-4}alkoxycarbonyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen; and

R^8 is selected from halo.

Y is hydrogen, methyl, ethyl, propyl, isopropyl, pentyl, butyl, *t*-butyl, allyl, ethynyl, phenyl, naphthyl, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthyl, indenyl, thienyl, furyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, pyrazolyl, isoxazolyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2*H*-indazolyl, imidazo[2,1-*b*][1,3]thiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, 2,3-dihydro-1-benzofuryl, 2,3-dihydro-1,4-benzodioxinyl or pyridyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said pyrrolyl, indolyl, piperidinyl, morpholinyl or pyrazolyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from fluoro, chloro, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, methyl, ethyl, *t*-butyl, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, *t*-butoxy, acetyl, methylamino, dimethylamino, acetamido, methylthio, mesyl, *t*-butoxycarbonylamino, *N*-(*t*-butoxycarbonyl)-*N*-(butyl)amino, phenyl, thienyl, isoxazolyl, morpholino, pyridyl, pyrazolyl, pyrrolidinyl, indolyl, 1,3-benzodioxolyl, isoindolinyl, pyrrolyl, phenoxy, phenylthio, benzyloxy, benzoyl, benzyloxycarbonylamino, thienylcarbonyl, pyrimidin-2-ylthio and morpholinosulphonyl; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from fluoro, chloro, bromo, nitro, methyl, ethenyl, methoxy, *t*-butoxyoxycarbonylamino, phenyl, phenoxy and benzoyl; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from methyl, ethyl and *t*-butoxycarbonyl; and

R^8 is selected from bromo.

Y is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, pentyl, naphthyl, phenyl, pyridyl, thienyl, furyl, cyclopropyl, cyclohexyl, thiazolyl, pyrazinyl, pyrrolyl, indolyl, quinolinyl, pyrazolyl, isoxazolyl, isoquinolinyl, indenyl, 1,2,3,4-tetrahydronaphthyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, morpholinyl, piperidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, isoindolinyl, tetrahydrofuryl, imidazo[2,1-b][1,3]thiazolyl, cyclopentyl, 2,3-dihydro-1,4-benzodioxinyl, tetrahydropyranyl,

2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, benzothienyl, chromanyl, 1,2,3,4-tetrahydroquinolinyl, 1,3-benzothiazolyl, 3,4-dihydro-2H-benzodioxepinyl, (3r)-adamantanyl, pyrrolidinyl, oxazolyl, 4,5,6,7-tetrahydro-1H-indolyl, quinoxalinyl or 4,5,6,7-tetrahydro-1-benzofuryl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if any heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

R^2 is fluoro, chloro, bromo, cyano, trifluoromethyl, nitro, amino, methyl, ethyl, isopropyl, *t*-butyl, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, *t*-butoxy, acetyl, phenyl, thienyl, morpholino, isoxazolyl, pyrazolyl, pyridyl, pyrrolidinyl, methylamino, isopropylamino, butylamino, dimethylamino, methylthio, mesyl, indolyl, morpholinosulphonyl, acetylamino, benzyloxy, 1,3-benzodioxolyl, thienylcarbonyl, phenoxy, phenylthio, pyrimidinylthio, *t*-butoxycarbonylamino, trifluoromethoxy, benzoyl, pyrrolyl, *N*-butyl-*N*-*t*-butoxycarbonylamino, *N*-methyl-*N*-*t*-butoxycarbonylamino, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-(*t*-butyl)sulphamoyl, piperidinyl, dimethylaminothiocarbonylthio, pyridazinyl or anilino; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is fluoro, chloro, bromo, cyano, nitro, trifluoromethyl, methyl, isopropyl, *t*-butyl, methoxy, ethoxy, *t*-butoxy, methylthio, phenyl, phenoxy, ethenyl, *t*-butoxycarbonylamino, dimethylamino or morpholino; wherein R^6 may be optionally substituted on carbon by one or more R^8

R^5 is selected from methyl, ethyl, *t*-butoxycarbonyl and acetyl;

Z is $-S(O)_a-$, -O-, $-NR^{10}-$, -C(O)- or $-OC(O)NR^{10}-$; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen; and

R^8 is bromo.

X and Y together form 6-chloronaphth-2-ylmethyl, benzyl, thien-2-ylmethyl, carbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diisopropylcarbamoyl, *N*-(phenyl)carbamoyl, *N*-(2-fluorophenyl)carbamoyl, *N*-(4-fluorophenyl)carbamoyl, *N*-(3,4-difluorophenyl)carbamoyl, *N*-(3-chlorophenyl)carbamoyl, *N*-(3-methylphenyl)carbamoyl, *N*-(benzyl)carbamoyl, morpholinocarbonyl, piperidin-1-ylcarbonyl, pyrid-4-yl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-methoxyphenyl, pyrimidin-2-yl, phenoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, 2-methoxyethoxycarbonyl, benzyloxycarbonyl, isopropoxycarbonyl, 4-fluorophenoxycarbonyl, 4-methoxyphenoxycarbonyl,

pyrrol-2-ylcarbonyl, 4-bromopyrrol-2-ylcarbonyl, 1-methylpyrrol-2-ylcarbonyl, 4-nitropyrrol-2-ylcarbonyl, 1,5-dimethylpyrrol-2-ylcarbonyl, 2,5-dimethylpyrrol-3-ylcarbonyl, thien-2-ylcarbonyl, thien-3-ylcarbonyl, 3-chlorothien-2-ylcarbonyl, 3-methylthien-2-ylcarbonyl, 5-chlorothien-2-ylcarbonyl, 3-bromothien-2-ylcarbonyl, 5-bromothien-2-ylcarbonyl, 5-methylthien-2-ylcarbonyl, 2-chloro-3-methoxythien-4-ylcarbonyl, thien-2-ylmethylcarbonyl, 5-mesylthien-2-ylcarbonyl, fur-2-ylcarbonyl, 5-bromofur-2-ylcarbonyl, 3-methylfur-2-ylcarbonyl, fur-3-ylcarbonyl, 2,5-dimethylfur-3-ylcarbonyl, 2,3-dimethylfur-5-ylcarbonyl, 2-methylfur-3-ylcarbonyl, 2-methyl-5-*t*-butylfur-3-ylcarbonyl, 5-trifluoromethylfur-2-ylcarbonyl, pyrid-2-ylcarbonyl, cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, benzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-ethylbenzoyl, 3-ethylbenzoyl, 4-ethylbenzoyl, 4-*t*-butylbenzoyl, 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-(*t*-butoxycarbonylamino)benzoyl, 4-(*t*-butoxycarbonylamino)benzoyl, 2,3-difluorobenzoyl, 2,4-difluorobenzoyl, 2,5-difluorobenzoyl, 3,4-difluorobenzoyl, 3,5-difluorobenzoyl, 2,3,4-trifluorobenzoyl, 3,4,5-trifluorobenzoyl, 2,4,5-trifluorobenzoyl, 2,3,4,5-tetrafluorobenzoyl, 2-cyanobenzoyl, 3-cyanobenzoyl, 4-cyanobenzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 2,3,4-trimethoxybenzoyl, 2,4,6-trimethoxybenzoyl, 2-ethoxybenzoyl, 3-ethoxybenzoyl, 4-ethoxybenzoyl, 3-propoxybenzoyl, 4-ispropoxybenzoyl, 3-(isobutoxy)benzoyl, 3-(*t*-butoxy)benzoyl, 4-(*t*-butoxy)benzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 4-methylaminobenzoyl, 4-dimethylaminobenzoyl, 2-methylthiobenzoyl, 4-methylthiobenzoyl, 2-nitrobenzoyl, 4-nitrobenzoyl, 3-(benzyloxycarbonylamino)benzoyl, 2-(phenethyl)benzoyl, 2-(phenoxymethyl)benzoyl, 4-(phenoxymethyl)benzoyl, 2-(trifluoromethoxy)benzoyl, 3-(trifluoromethoxy)benzoyl, 3-phenoxybenzoyl, 4-phenoxybenzoyl, 3-benzoylbenzoyl, 3-benzyloxybenzoyl, 3-(allyloxy)benzoyl, 4-pyrrol-1-ylbenzoyl, 4-(*t*-butoxycarbonylaminomethyl)benzoyl, 4-[*N*-(*t*-butoxycarbonyl)-*N*-(butyl)amino]benzoyl, 2-fluoro-5-methoxybenzoyl, 3-fluoro-4-methoxybenzoyl, 5-fluoro-2-methoxybenzoyl, 3-fluoro-4-methylbenzoyl, 2-methyl-3-fluorobenzoyl, 2-chloro-3-methoxybenzoyl, 2-methoxy-3-methylbenzoyl, 3-methoxy-4-methylbenzoyl, 2-methoxy-4-methylbenzoyl, 2-methyl-3-methoxybenzoyl, 2-methyl-4-methoxybenzoyl, 3-methyl-4-methoxybenzoyl, 2,4-dimethoxy-3-methylbenzoyl,

3-(morpholinosulphonyl)benzoyl, 4-(morpholinosulphonyl)benzoyl, 3-benzyloxy-4-methoxybenzoyl, 2-ethylbutyryl, 4-(2,4-dimethylphenyl)butyryl, 4-(indol-3-yl)butyryl, 4-(5-bromothien-2-ylcarbonyl)butyryl, 4-morpholinobenzoyl, isoxazole-5-ylcarbonyl, 3-methylisoxazole-5-ylcarbonyl, 3,5-dimethylisoxazol-4-ylcarbonyl, 4-(pyrazol-1-yl)benzoyl, thiazol-4-ylcarbonyl, 2-methylthiazol-4-ylcarbonyl, 3-chlorothiazol-5-ylcarbonyl, 2,4-dimethylthiazol-5-ylcarbonyl, 2-(pyrid-2-yl)-4-methylthiazol-5-ylcarbonyl, 2-(pyrrolidin-1-yl)pyrazin-6-ylcarbonyl, 2-phenylbenzoyl, 4-phenylbenzoyl, 2-(2-nitrophenyl)benzoyl, 3-(4-fluorophenyl)benzoyl, 4-acetylbenzoyl, indol-6-ylcarbonyl, indol-7-ylcarbonyl, 5-fluoroindol-2-ylcarbonyl, 1-methylindol-3-ylcarbonyl, 3-methylindol-1-ylcarbonyl, 5-methoxyindol-2-ylcarbonyl, isoquinoline-1-ylcarbonyl, quinoline-2-ylcarbonyl, quinoline-3-ylcarbonyl, quinoline-4-ylcarbonyl, quinoline-6-ylcarbonyl, 2-methylquinoline-6-ylcarbonyl, 3-methylinden-2-ylcarbonyl, 1,2,3,4-tetrahydronaphth-5-ylcarbonyl, benzofuran-2-ylcarbonyl, 1,2,3-thiadiazol-4-ylcarbonyl, 1,2,5-thiadiazol-3-ylcarbonyl, pyrazol-3-ylcarbonyl, 1-methylpyrazol-3-ylcarbonyl, 5-methylpyrazol-3-ylcarbonyl, 1,5-dimethylpyrazol-3-ylcarbonyl, 1-ethyl-3-methylpyrazol-5-ylcarbonyl, 1-methyl-5-chloropyrazol-4-ylcarbonyl, 1-methyl-3-*t*-butylpyrazol-5-ylcarbonyl, 2,1-benzisoxazol-3-ylcarbonyl, 2-(2-chlorophenyl)ethynylcarbonyl, 3-(5-bromo-1,3-benzodioxol-6-yl)propionyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 2-ethylheptanoyl, 4,5,6,7-tetrahydro-2*H*-indazol-3-ylcarbonyl, 6-methylimidazo[2,1-*b*][1,3]thiazol-5-ylcarbonyl, *N*-(*t*-butoxycarbonyl)piperidin-3-ylcarbonyl, *N*-(*t*-butoxycarbonyl)piperidin-4-ylcarbonyl, *N*-(*t*-butoxycarbonyl)morpholin2-ylcarbonyl, tetrahydrofuran-2-ylcarbonyl, tetrahydrofuran-3-ylcarbonyl, 2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl, tetrahydropyranylcarbonyl, 2,3-dihydro-1-benzofur-2-ylcarbonyl, acetyl, (3,5-dimethylisoxazol-4-yl)acetyl, (4-fluorophenyl)acetyl, (2-nitrophenyl)acetyl, (4-bromobenzoylmethylthio)acetyl, (2,4-dichloro-6-methoxyphenoxy)acetyl, (2-nitro-4-chlorophenylthio)acetyl, (pyrimidin-2-ylthio)acetyl, (isoindolin-2-yl)acetyl, thien-2-ylsulphonyl, mesyl, ethylsulphonyl, isopropylsulphonyl, butylsulphonyl, 2-methylphenylsulphonyl, 3-methylphenylsulphonyl, 4-methylphenylsulphonyl, 2,5-dimethylphenylsulphonyl, 4-ethylphenylsulphonyl, 3-methoxyphenylsulphonyl, 4-methoxyphenylsulphonyl, 2-fluorophenylsulphonyl, 3-fluorophenylsulphonyl, 4-fluorophenylsulphonyl, 2-chlorophenylsulphonyl, 3-chlorophenylsulphonyl,

4-chlorophenylsulphonyl, 2-bromophenylsulphonyl, 3-bromophenylsulphonyl, 4-bromophenylsulphonyl, 2-trifluoromethylsulphonyl, 3-trifluoromethylsulphonyl, 4-trifluoromethylsulphonyl, 4-acetamidophenylsulphonyl, 2,4-difluorophenylsulphonyl, 2,6-difluorophenylsulphonyl, 2,4,5-trifluorophenylsulphonyl, 2-cyanophenylsulphonyl, 2-chloro-4-fluorophenylsulphonyl, 2-chloro-6-methylphenylsulphonyl, 3-fluoro-6-methylphenylsulphonyl, 2-methoxy-5-methylphenylsulphonyl, 2-nitro-4-methoxyphenylsulphonyl, 3-chloro-4-aminophenylsulphonyl, 2-chloro-4-cyanophenylsulphonyl, benzylsulphonyl, 4-fluorobenzylsulphonyl, thien-3-ylsulphonyl, 5-chlorothien-2-ylsulphonyl, 2,5-dichlorothien-3-ylsulphonyl, 1,3-dimethyl-5-chloropyrazol-4-ylsulphonyl, 3,5-dimethylisoxazol-4-ylsulphonyl and (4-fluoroanilino)thiocarbonyl.

X and Y together form hydrogen, *t*-butoxycarbonyl, carbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diisopropylcarbamoyl, acetyl, mesyl, isopropylsulphonyl, ethylsulphonyl, butylsulphonyl, methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, 2-methoxyethoxycarbonyl, isopropylcarbonyl, hept-3-ylcarbonyl, *t*-butylcarbonyl, pent-3-ylcarbonyl, isopropoxycarbonyl, dimethylaminothiocarbonylthioacetyl, 3,3,3-trifluoropropionyl, 4,4,4-trifluorobutyryl, 2-methyl-4,4,4-trifluorobutyryl, 2-(*t*-butoxycarbonylamino)acetyl, 2-(*N*-methyl-*t*-butoxycarbonylamino)acetyl, 2-aminoacetyl, pyrid-4-yl, 4-fluorophenyl, pyrimidin-2-yl, 4-trifluoromethylphenyl, 4-acetylphenyl, 4-acetylaminophenyl, 4-methoxyphenyl, 6-chloronaphth-2-ylmethyl, benzyl, thien-2-ylmethyl, 4-acetylbenzoyl, 3-allyloxybenzoyl, 2-aminobenzoyl, 3-benzoylbenzoyl, 3-benzyloxybenzoyl, 4-benzyloxybenzoyl, 3-(benzyloxycarbonylamino)benzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, benzoyl, 4-(*N*-butyl-*t*-butoxycarbonylamino)benzoyl, 2-*t*-butoxycarbonylaminobenzoyl, 4-*t*-butoxycarbonylaminobenzoyl, 4-(*t*-butoxycarbonylaminomethyl)benzoyl, 3-*t*-butoxybenzoyl, 4-*t*-butoxybenzoyl, 4-butylaminobenzoyl, 4-*t*-butylbenzoyl, 4-difluoromethoxybenzoyl, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-cyanobenzoyl, 3-cyanobenzoyl, 4-cyanobenzoyl, 2-difluoromethoxybenzoyl, 4-difluoromethoxybenzoyl, 4-dimethylaminobenzoyl, 4-(3-dimethylaminopyridazin-6-yl)benzoyl, benzoyl, 2-ethoxybenzoyl, 3-ethoxybenzoyl, 4-ethoxybenzoyl, 4-(2-ethoxyethoxy)benzoyl, 2-ethylbenzoyl, 3-ethylbenzoyl, 4-ethylbenzoyl, 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 3-(4-fluorophenyl)benzoyl, 3-isobutoxybenzoyl, 4-isopropoxybenzoyl,

4-isopropylaminobenzoyl, 2-isopropylbenzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2-methylbenzoyl, 4-methylaminobenzoyl, 4-methylbenzoyl, 2-methylthiobenzoyl, 4-methylthiobenzoyl, 4-morpholinobenzoyl, 3-morpholinosulphonylbenzoyl, 4-morpholinosulphonylbenzoyl, 2-nitrobenzoyl, 4-nitrobenzoyl, 2-(2-nitrophenyl)benzoyl, 2-phenethylbenzoyl, 3-phenoxybenzoyl, 4-phenoxybenzoyl, 2-phenoxymethylbenzoyl, 2-phenylbenzoyl, 4-phenylbenzoyl, 4-piperidin-1-ylbenzoyl, 3-propoxybenzoyl, 4-pyrazol-1-ylbenzoyl, 4-pyrrol-1-ylbenzoyl, 2-trifluoromethoxybenzoyl, 3-trifluoromethoxybenzoyl, 4-trifluoromethoxybenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 2,3-difluorobenzoyl, 2,4-difluorobenzoyl, 2,5-difluorobenzoyl, 3,4-difluorobenzoyl, 3,5-difluorobenzoyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 3,5-ditrifluoromethylbenzoyl, 2-(3-trifluoromethylanilino)benzoyl, 2-fluoro-6-methoxybenzoyl, 2-fluoro-4-chlorobenzoyl, 2-fluoro-4-cyanobenzoyl, 2-fluoro-5-methoxybenzoyl, 2-fluoro-5-trifluoromethylbenzoyl, 2-fluoro-5-methylbenzoyl, 3-fluoro-4-methoxybenzoyl, 3-fluoro-4-methylbenzoyl, 3-fluoro-4-trifluoromethylbenzoyl, 2-methyl-3-fluorobenzoyl, 2-methyl-4-methoxybenzoyl, 2-methyl-3-methoxybenzoyl, 3-methyl-4-methoxybenzoyl, 2-methoxy-3-fluorobenzoyl, 2-methoxy-5-fluorobenzoyl, 2-methoxy-4-methylbenzoyl, 2-methoxy-3-methylbenzoyl, 2-methoxy-4-chlorobenzoyl, 3-methoxy-4-methylbenzoyl, 3-methoxy-4-chlorobenzoyl, 3-benzyloxy-4-methoxybenzoyl, 2-(*t*-butylsulphamoyl)-5-chlorobenzoyl, 2-trifluoromethyl-4-fluorobenzoyl, 3-trifluoromethyl-4-fluorobenzoyl, 3-trifluoromethyl-4-methoxybenzoyl, 3-trifluoromethyl-4-methylbenzoyl, 3-trifluoromethyl-4-chlorobenzoyl, 2-chloro-4-fluorobenzoyl, 2-chloro-5-fluorobenzoyl, 2-chloro-3-methoxybenzoyl, 2-chloro-5-trifluoromethylbenzoyl, 2-chloro-5-(pyrrol-1-yl)benzoyl, 2-chloro-4-morpholinobenzoyl, 3-chloro-4-fluorobenzoyl, 3-chloro-4-trifluoromethoxybenzoyl, 3-mesyl-4-chlorobenzoyl, 2,3,4-trifluorobenzoyl, 2,4,5-trifluorobenzoyl, 3,4,5-trifluorobenzoyl, 2,3,4-trimethoxybenzoyl, 2,4,6-trimethoxybenzoyl, 2,4-dimethoxy-3-methylbenzoyl, 2-chloro-4,5-dimethoxybenzoyl, 2,3,4,5-tetrafluorobenzoyl, cyclopropylcarbonyl, 1-phenylcyclopropylcarbonyl, 1-(4-methoxyphenyl)cyclopropylcarbonyl, cyclopentylcarbonyl, 1-phenylcyclopentlycarbonyl, cyclohexylcarbonyl, 4-(4-chlorophenoxy)cyclohexylcarbonyl, 4,4-difluorocyclohexylcarbonyl, 3-methylinden-2-ylcarbonyl, 1,2,3,4-tetrahydronaphth-5-ylcarbonyl, (3r)-adamantan-1-ylcarbonyl, thien-2-ylcarbonyl,

thien-3-ylcarbonyl, 2-chloro-3-methoxylthien-4-ylcarbonyl, 3-methylthien-2-ylcarbonyl, 5-methylthien-2-ylcarbonyl, 3-chlorothien-2-ylcarbonyl, 5-chlorothien-2-ylcarbonyl, 5-bromothien-2-ylcarbonyl, 3-bromothien-2-ylcarbonyl, 5-mesylthien-2-ylcarbonyl, 5-(pyrid-2-yl)thien-2-ylcarbonyl, 5-acetylthien-2-ylcarbonyl, 5-methylthiothien-2-ylcarbonyl, fur-2-ylcarbonyl, fur-3-ylcarbonyl, 5-bromofur-2-ylcarbonyl, 5-trifluoromethylfur-2-ylcarbonyl, 3-methylfur-2-ylcarbonyl, 5-ethoxyfur-2-ylcarbonyl, 2-methyl-5-*t*-butylfur-3-ylcarbonyl, 2,5-dimethylfur-3-ylcarbonyl, 2,3-dimethylfur-5-ylcarbonyl, 2-methylfur-3-ylcarbonyl, 5-methylfur-2-ylcarbonyl, 5-(4-chlorophenyl)fur-2-ylcarbonyl, 5-(dimethylaminomethyl)fur-2-ylcarbonyl, 5-(morpholinomethyl)fur-2-ylcarbonyl, 5-phenylfur-2-ylcarbonyl, 2-trifluoromethyl-5-phenylfur-3-ylcarbonyl, 2-methyl-5-(*N,N*-dimethylsulphamoyl)fur-3-ylcarbonyl, thiazol-4-ylcarbonyl, 2-methylthiazol-4-ylcarbonyl, 2-phenylthiazol-4-ylcarbonyl, 2-(4-chlorophenyl)thiazol-4-ylcarbonyl, thiazol-5-ylcarbonyl, 2-phenyl-4-methylthiazol-5-ylcarbonyl, 2-chlorothiazol-5-ylcarbonyl, 2,4-dimethylthiazol-5-ylcarbonyl, 2-(pyrid-2-yl)-4-methylthiazol-5-ylcarbonyl, 2-(4-trifluoromethylphenyl)-4-methylthiazol-5-ylcarbonyl, pyrazin-2-ylcarbonyl, 2-methylaminopyrazin-6-ylcarbonyl, 2-(pyrrolidin-1-yl)pyrazin-6-ylcarbonyl, pyrrol-2-ylcarbonyl, 1-methylpyrrol-2-ylcarbonyl, 4-bromopyrrol-2-ylcarbonyl, 1,2-dimethylpyrrol-5-ylcarbonyl, 1,5-dimethylpyrrol-3-ylcarbonyl, 4-nitropyrrol-2-ylcarbonyl, indol-2-ylcarbonyl, 1-acetylindol-2-ylcarbonyl, 5-fluoroindol-2-ylcarbonyl, 5-trifluoromethoxyindol-2-ylcarbonyl, 5,7-difluoroindol-2-ylcarbonyl, indol-5-ylcarbonyl, indol-6-ylcarbonyl, indol-7-ylcarbonyl, 1-methylindol-3-ylcarbonyl, 1-methylindol-7-ylcarbonyl, quinoline-2-ylcarbonyl, quinoline-3-ylcarbonyl, quinoline-4-ylcarbonyl, quinoline-6-ylcarbonyl, 2-methylquinolin-6-ylcarbonyl, pyrid-2-ylcarbonyl, 3-methylpyrid-2-ylcarbonyl, 6-methylpyrid-2-ylcarbonyl, 3-propoxypyrid-2-ylcarbonyl, 3-(4-chlorobenzoyl)pyrid-2-ylcarbonyl, 3-chloro-5-trifluoromethylpyrid-2-ylcarbonyl, pyrid-3-ylcarbonyl, 6-trifluoromethylpyrid-3-ylcarbonyl, 4-trifluoromethylpyrid-3-ylcarbonyl, 2-(3-trifluoromethylanilino)pyrid-3-ylcarbonyl, isoquinolin-1-ylcarbonyl, benzofuran-2-ylcarbonyl, 2-methylbenzofuran-6-ylcarbonyl, isoxazol-5-ylcarbonyl, 3-methylisoxazol-5-ylcarbonyl, 3,5-dimethylisoxazol-4-ylcarbonyl, 1,2,3-thiadiazol-4-ylcarbonyl, 1,2,5-thiadiazol-3-ylcarbonyl, pyrazol-3-ylcarbonyl,

1-methylpyrazol-3-ylcarbonyl, 5-methylpyrazol-3-ylcarbonyl, 1,5-dimethylpyrazol-3-ylcarbonyl, 1-ethyl-3-methylpyrazol-5-ylcarbonyl, 1-methyl-5-chloropyrazol-3-ylcarbonyl, 1-methyl-3-*t*-butylpyrazol-5-ylcarbonyl, morpholinocarbonyl, piperidin-1-ylcarbonyl, 4-(4-fluorobenzoyl)piperidin-1-ylcarbonyl, 1-(*t*-butoxycarbonyl)-4-phenylpiperidin-4-ylcarbonyl, 2,1-benzisoxazol-3-ylcarbonyl, 4,5,6,7-tetrahydro-2H-indazol-3-ylcarbonyl, 6-methylimidazo[2,1-b][1,3]thiazol-5-ylcarbonyl, 1-(*t*-butoxycarbonyl)-piperdin-3-ylcarbonyl, 1-(*t*-butoxycarbonyl)-piperdin-4-ylcarbonyl, tetrahydrofur-2-ylcarbonyl, tetrahydrofur-2-ylcarbonyl, tetrahydrofur-3-ylcarbonyl, 2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl, 4-(*t*-butoxycarbonyl)-morpholin-2-ylcarbonyl, tetrahydropyran-4-ylcarbonyl, 2,3-dihydrobenzofuran-2-ylcarbonyl, 2,3-dihydrobenzofuran-5-ylcarbonyl, 2,3-dihydrobenzofuran-7-ylcarbonyl, 1,3-benzodioxol-4-ylcarbonyl, 1,3-benzodioxol-5-ylcarbonyl, 2,2-difluoro-1,3-benzodioxol-4-ylcarbonyl, 2,2-difluoro-1,3-benzodioxol-5-ylcarbonyl, benzothien-2-ylcarbonyl, chroman-2-ylcarbonyl, 2,2-dimethylchroman-6-ylcarbonyl, 1,2,3,4-tetrahydroquinolin-6-ylcarbonyl, 1,3-benzothiazol-6-ylcarbonyl, 3,4-dihydro-2H-benzodioxepin-7-ylcarbonyl, pyrrolidin-1-ylcarbonyl, 2-phenyl-5-trifluoromethyloxazol-4-ylcarbonyl, 2-methyl-5-trifluoromethyloxazol-4-ylcarbonyl, 4,5,6,7-tetrahydro-1H-indol-2-ylcarbonyl, quinoxaline-2-ylcarbonyl, 2-methyl-4,5,6,7-tetrahydro-1-benzofur-3-ylcarbonyl, 2-(thien-2-yl)acetyl, 2-(3,5-dimethylisoxazol-4-yl)acetyl, 2-(4-fluorophenyl)acetyl, 2-(4-trifluoromethylphenyl)acetyl, 2-(2-nitrophenyl)acetyl, 2-(4-bromobenzoylmethylthio)acetyl, 2-(2,4-dichloro-6-methoxyphenoxy)acetyl, 2-(pyrimidin-2-ylthio)acetyl, 2-(isoindolin-2-yl)acetyl, 2-(phenoxy)acetyl, 2-(4-fluorophenoxy)acetyl, 2-(4-isopropylphenoxy)acetyl, 2-(3-chlorophenoxy)acetyl, 2-(3-methoxyphenoxy)acetyl, 2-(4-*t*-butylphenoxy)acetyl, 2-(*t*-butoxyphenoxy)acetyl, 2-(4-cyanophenoxy)acetyl, 2-(3-trifluoromethylphenoxy)acetyl, 2-(4-methylthiophenoxy)acetyl, 2-(3,5-dichlorophenoxy)acetyl, 2-(2-trifluoromethylphenyl)acetyl, 2-(3-trifluoromethyl-4-fluorophenyl)acetyl, 2-(3-trifluoromethyl-5-fluorophenyl)acetyl, 2-(3,5-ditrifluoromethylphenyl)acetyl, 4-(2,4-dimethylphenyl)butyryl, 4-indol-3-ylbutyryl, 4-(5-bromothien-2-ylcarbonyl)butyryl, 2-(4-chlorophenoxy)-2-(methyl)butyryl, 3-(2-chlorophenyl)propioloyl, 3-(5-bromo-1,3-benzodioxol-6-yl)propionyl, 3-(3-methylindol-1-yl)propionyl,

3-(4-trifluoromethylphenyl)propionyl, 2-(4-chlorophenoxy)propionyl, 2-(4-chlorophenyl)-2-(methyl)propionyl, 2-(4-chlorophenoxy)-2-(methyl)propionyl, 2-(phenoxy)-2-(methyl)propionyl, 2-(3-trifluoromethylphenoxy)-2-(methyl)propionyl, 4-acetylaminophenylsulphonyl, 2-bromophenylsulphonyl, 3-bromophenylsulphonyl, 4-bromophenylsulphonyl, 4-chlorophenylsulphonyl, 2-cyanophenylsulphonyl, 4-ethylphenylsulphonyl, 2-fluorophenylsulphonyl, 3-fluorophenylsulphonyl, 4-fluorophenylsulphonyl, 2-chlorophenylsulphonyl, 3-chlorophenylsulphonyl, 3-methoxyphenylsulphonyl, 4-methoxyphenylsulphonyl, 2-methylphenylsulphonyl, 3-methylphenylsulphonyl, 4-methylphenylsulphonyl, 2-trifluoromethylphenylsulphonyl, 3-trifluoromethylphenylsulphonyl, 4-trifluoromethylphenylsulphonyl, 2,5-dimethylphenylsulphonyl, 2,4-difluorophenylsulphonyl, 2,6-difluorophenylsulphonyl, 2-chloro-4-fluorophenylsulphonyl, 2-methyl-5-fluorophenylsulphonyl, 2-methoxy-5-methylphenylsulphonyl, 2-methyl-6-chlorophenylsulphonyl, 2-nitro-4-methoxyphenylsulphonyl, 3-chloro-4-aminophenylsulphonyl, 2-chloro-4-cyanophenylsulphonyl, 2,4,5-trifluorophenylsulphonyl, thien-2-ylsulphonyl, thien-3-ylsulphonyl, 5-chlorothien-2-ylsulphonyl, 2,5-dichlorothien-3-ylsulphonyl, 1,3-dimethyl-5-chloropyrazol-4-ylsulphonyl, 3,5-dimethylisoxazol-4-ylsulphonyl, benzylsulphonyl, 4-fluorobenzylsulphonyl, anilinocarbonyl, *N*-methylanilinocarbonyl, 2-fluoroanilinocarbonyl, 4-fluoroanilinocarbonyl, 4-fluoroanilinothiocarbonyl, 3-chloroanilinocarbonyl, 3-methylanilinocarbonyl, 2-ethylanilinocarbonyl, 2-trifluoromethylanilinocarbonyl, 2,3-difluoroanilinocarbonyl, 2,5-difluoroanilinocarbonyl, 2,6-difluoroanilinocarbonyl, 3,4-difluoroanilinocarbonyl, 2,6-dimethylaniliocarbonyl, 4-(pyrid-2-yl)anilinocarbonyl, *N*-methyl-4-fluoroanilinocarbonyl, benzylaminocarbonyl, 4-methoxybenzylaminocarbonyl, 4-methylbenzylaminocarbonyl, 2-fluorobenzylaminocarbonyl, 3-fluorobenzylaminocarbonyl, phenoxycarbonyl, benzyloxycarbonyl, 4-fluorophenoxycarbonyl, 4-methoxyphenoxycarbonyl, [(1R)-1-phenylethyl]aminocarbonyl or iminophenylmethyl.

R^{12} is 4-methyl.

R^{12} is 4-ethyl.

R^{12} is 4-propyl.

R^{12} is 3-methyl.

m is 0.

m is 1.

q is 0.

q is 1.

According to a further feature of the invention there is provided the use of a compound of formula (I) wherein:

Ring A is phenyl;

R^1 is selected from halo or C_{1-4}alkyl;

n is 1;

X is -C(O)-, -S(O)$_2$- or -CH$_2$-;

Y is phenyl, thienyl, methyl, furyl, cyclopropyl or cyclohexyl; wherein Y may be optionally substituted on carbon by one or more R^2; and

R^2 is a substituent on carbon and is selected from halo or C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof;

q is 0;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

According to a further feature of the invention there is provided the use of a compound of formula (I) wherein:

Ring A is selected from phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl or furyl;

R^1 is a substituent on carbon and is selected from halo, C_{1-4}alkyl, C_{1-4}alkoxy, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein R^3 is halo; and Z is -S(O)$_a$-; wherein a is 2;

n is 0-2; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O- or -CH$_2$-; wherein R^{11} is selected from hydrogen and methyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 or 2, o, carbocyclyl

and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl and C_{1-4}alkoxycarbonyl;

R^8 is selected from halo; and

Z is -S(O)$_a$-, -O-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 or 2; wherein R^{10} is selected from hydrogen;

R^{12} is methyl or ethyl;

m is 0 or 1; and

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

According to a further feature of the invention there is provided the use of a compound of formula **(I)** wherein:

Ring A is phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl, furyl, thiazolyl, 1,3-benzothiazolyl, benzofuryl or benzothienyl;

R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein

R^3 is selected from halo, hydroxy, C_{1-4}alkoxy, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; and

Z is -S(O)$_a$- or -O-; wherein a is 0 to 2;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O-, -C(=NR^{11})- or -CH$_2$-; wherein $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-4}alkyl, carbocyclyl and heterocyclyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl,

heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, carbocyclyl, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl, C_{1-4}alkanoyl and C_{1-4}alkoxycarbonyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen; and

R^8 is selected from halo;

$\mathbf{R^{12}}$ is hydroxy, methyl, ethyl or propyl;

m is 0 or 1; and

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

In another aspect of the invention, suitable compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, suitable compounds of the invention are any one of the Reference Examples or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are Examples 57, 76, 101, 103, 161, 206, 210, 213, 215, 233 and 398 or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a compound selected from Group A:

1-[2-hydroxy-2-(2,3-dihydro-1,4-benzodioxin-2-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;
1-(7-methyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;
1-(6-fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;
1-(7-fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-(benzoyl)piperidine;
1-[2-(6-methoxynaphth-2-yl)propionyl]-4-(4-fluorobenzoyl)piperidine;
1-(4-bromoindol-2-ylcarbonyl)-4-(benzoyl)piperidine; and
1-(3-phenyl-5-methylisoxazol-4-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;
or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided the use of a compound selected from Group B:

1-[2-((1*H*,3*H*)-2,4-dioxoquinazolin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;
1-[3-(napath-1-yloxy)propyl]-4-(4-fluorobenzoyl)piperidine;
1-[2-(2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;
4-(4-fluorobenzoyl)piperidine;
1-(*t*-butoxycarbonyl)-4-(benzoyl)piperidine;
1-(acetyl)-4-(4-fluorobenzoyl)piperidine;
1-(*t*-butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine;
1-(2,4-trifluoromethyl-6-methoxybenzoyl)-4-(4-chlorobenzoyl)piperidine;
1-(3,4-dichlorophenylsulphonyl)-4-(4-methylbenzoyl)piperidine;
1-(2-nitro-4-trifluoromethylphenyl)-4-(benzoyl)piperidine;
1-(anilinocarbonyl)-4-(benzoyl)piperidine;
1-[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-ylcarbonyl]-4-(benzoyl)piperidine;
1-(4-chlorobenzoyl)-4-(benzoyl)piperidine;
1-[(5-trifluoromethylpyrid-2-ylthio)acetyl]-4-(benzoyl)piperidine;
1-[(4-chlorophenylthio)acetyl]-4-(benzoyl)piperidine;
1-(fur-2-ylcarbonyl)-4-(benzoyl)piperidine;
1-(4-methyl-1,2,3-thiadiazol-5-ylcarbonyl)-4-(benzoyl)piperidine;
1-(thien-2-ylcarbonyl)-4-(benzoyl)piperidine;
1-(3-trifluoromethylbenzoyl)-4-(benzoyl)piperidine;
1-(propylaminothiocarbonyl)-4-(4-methylbenzoyl)piperidine;
1-(5-nitrofur-2-ylcarbonyl)-4-(2,3,4,5,6-pentamethylbenzoyl)piperidine;
1-(3,5-ditrifluoromethylphenylsulphonyl)-4-(4-methylbenzoyl)piperidine;
1-(3,5-dimethylisoxazol-4-ylsulphonyl)-4-(4-methylbenzoyl)piperidine;
1-(2,6-difluorobenzoyl)-4-(benzoyl)piperidine;
1,4-bis-(4-methylbenzoyl)piperidine;
1-(3,5-ditrifluoromethylphenylsulphonyl)-4-(2,4-difluorobenzoyl)piperidine;
1-(2,4-difluorophenylsulphonyl)-4-(2,4-difluorobenzoyl)piperidine;
1-(4-methylbenzoyl)-4-(2,4,6-trimethylbenzoyl)piperidine;
1-(4-chlorophenylsulphonyl)-4-(benzoyl)piperidine;
1-[2-((1*H*,3*H*)-2-thiocarbonyl-4-oxoquinazolin-3-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;
1-(trifluoroacetyl)-4-(benzoyl)piperidine;

1-(3,5-dimethylisoxazol-4-ylsulphonyl)-4-(benzoyl)piperidine;

1-(4-*t*-butylbenzoyl)-4-(benzoyl)piperidine;

1-(2,4-dimethylthiazol-5-ylsulphonyl)-4-(benzoyl)piperidine;

1-[(4-chlorophenylsulphonyl)acetyl]-4-(benzoyl)piperidine;

1-(4-chloroanilinocarbonyl)-4-(benzoyl)piperidine;

1-[3-methyl-4-(4-chlorophenylsulphonyl)thien-2-ylcarbonyl]-4-(4-fluorobenzoyl)piperidine;

1-(thien-2-ylcarbonyl)-4-(2,4-difluorobenzoyl)piperidine;

1-[1-(4-isobutylphenyl)ethyl]-4-(benzoyl)piperidine;

1-{1-[4-(4-trifluoromethylphenoxy)phenoxy]ethyl}-4-(benzoyl)piperidine;

1-(3,5-ditrifluoromethylanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;

1-(2-methyl-4-bromoanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;

1-(4-fluoroanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;

1-(thien-2-ylcarbonyl)-4-(2,4,6-trimethylbenzoyl)piperidine;

1-(cyclobutylcarbonyl)-4-(benzoyl)piperidine;

1-(2,4-dichloroanilinothiocarbonyl)-4-(4-methylbenzoyl)piperidine;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

In a further aspect of the invention there is provided a compound selected from Group C:

1-[2-(6-fluoro-2,3-dihydro-1,4-benzodioxin-2-yl)-2-hydroxyethyl]-4-benzoylpiperidine;

1-[2-(5-fluoro-2,3-dihydro-1,4-benzodioxin-2-yl)-2-hydroxyethyl]-4-(4-fluorobenzoyl) piperidine;

1-[3-(4-fluorophenoxy)-2-hydroxypropyl]-4-benzoylpiperidine;

1-[2-(S)-(2-(S)-5,6-difluoro-2,3-dihydro-1,4-benzodioxin-2-yl)-2-hydroxyethyl]-4-benzoylpiperidine;

1-(5-fluoro-2,3-dihydro-1,4-benzodioxin-2-ylmethyl-4-benzoylpiperidine;

1-[3-(9,10-dihydro-9,10-methanoanthracen-9-ylmethylamino)propyl]-4-(2-methoxybenzoyl) piperidine;

1-[3-(2-chloro-9,10-dihydro-9,10-methanoanthracen-9-ylmethylamino)propyl]-4-benzoylpiperidine;

1-(5-methyl-4-cyano-4-phenylhexyl)-4-(4-chlorobenzoyl)piperidine;

1-(2,4-difluorophenylsulphonyl)-4-(2,3,4,5,6-pentamethylbenzoyl)piperidine;

1-[*N*-(1-methyl-3-phenylpyrazol-5-yl)carbamoylmethyl]-4-(4-chlorobenzoyl)piperidine;

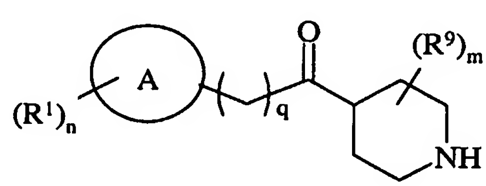
1-[*N*-(3-methyl-4-bromoisoxazol-5-ylcarbamoyl)methyl]-4-benzoylpiperidine;
1-(4,6-dimethylindol-2-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;
1-[5-(thien-2-yl)thien-2-ylcarbonyl]-4-(4-fluorobenzoyl)piperidine;
1-(*t*-butoxycarbonyl)-4-hydroxy-4-(2-fluorobenzoyl)piperidine;
or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided the use of a compound selected from Group D:

1-[2-(1,3-dioxo-2,4-dihydroquinazolin-2-yl)ethyl]-4-(4-fluorobenzoyl)piperidine;
1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-benzoylpiperidine;
1-(2-chloro-9,10-dihydro-9,10-methanoanthracen-9-ylmethyl)-4-(pyrid-3-yl)piperidine;
1-(*t*-butoxycarbonyl)-4-(pyrid-3-yl)piperidine;
1-(3-nitropyrid-2-yl)-4-benzoylpiperidine;
1-(5-nitropyrid-2-yl)-4-benzoylpiperidine;
1-(5-nitropyrid-2-yl)-4-(4-fluorobenzoyl)piperidine;
1-(5-nitropyrid-2-yl)-4-(4-methylbenzoyl)piperidine;
1-(5-nitropyrid-2-yl)-4-(2,4-difluorobenzoyl)piperidine;
1-(2-nitro-4-acetylphenyl)-4-benzoylpiperidine;
1-benzylcarbonyl-4-benzoylpiperidine;
or a pharmaceutically acceptable salt thereof;
in the manufacture of a medicament for use in the inhibition of 11βHSD1.

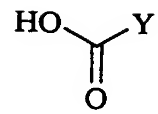
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

Process 1) for compounds of formula (I) wherein X is -C(O)-; reacting an amine of formula (II):



(II)

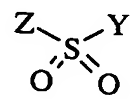
with an acid of formula (III):



(III)

or an activated derivative thereof;

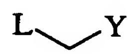
Process 2) for compounds of formula **(I)** wherein X is -$S(O)_2$-; reacting an amine of formula **(II)** with a sulphonyl halide of formula **(IV)**:



(IV)

wherein Z is fluoro or chloro;

Process 3) for compounds of formula **(I)** wherein X is -CH_2-; reacting an amine of formula **(II)** with a compound of formula **(V)**:



(V)

wherein L is a displaceable group; or

Process 4) for compounds of formula **(I)** wherein X is -CH_2-; reducing a compound of formula **(I)** wherein X is -C(O)-;

Process 5) for compounds of formula **(I)** wherein X is a direct bond; reacting an amine of formula **(II)** with a compound of formula **(VI)**:

L-Y

(VI)

Process 6) for compounds of formula **(I)** wherein X is -C(O)NR^{11}- and R^{11} is hydrogen; reacting an amine of formula **(II)** with an isocyanate of formula **(VII)**:

O=C=N-Y

(VII)

Process 7) for compounds of formula **(I)** wherein X is -C(S)NR^{11}- and R^{11} is hydrogen; reacting an amine of formula **(II)** with an isothiocyanate of formula **(VIII)**:

S=C=N-Y

(VIII)

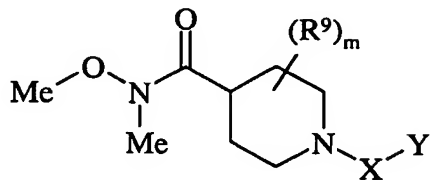
Process 8) for compounds of formula **(I)** wherein X is -C(O)O-; reacting an amine of formula **(II)** with a compound of formula **(IX)**:

L-C(O)-O-Y

(IX)

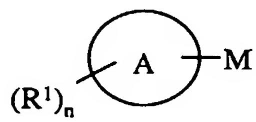
wherein L is a displaceable group;

Process 9) for compounds of formula **(I)** wherein q is 0; reacting a Weinreb amide of the formula **(X)**:



(X)

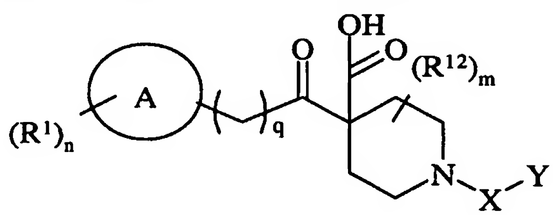
with a compound of formula **(XI)**:



(XI)

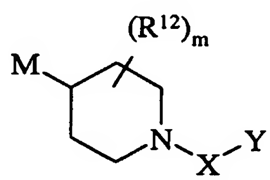
wherein M is an organometallic reagent;

Process 10) decarboxylating a compound of formula **(XII)**:



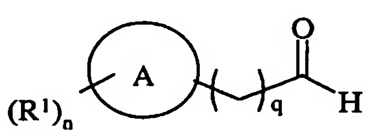
(XII)

Process 11) reacting a compound of formula **(XIII)**:



(XIII)

wherein M is an organometallic reagent, with a compound of formula **(XIV)**:



(XIV)

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);
ii) removing any protecting groups;
iii) forming a pharmaceutically acceptable salt thereof.

L is a displaceable group, suitable values for L include halo, particularly chloro or bromo, or mesyloxy.

M is an organometallic reagent, preferably a Grignard reagent, more preferably magnesium bromide.

The reactions described above may be performed under standard conditions known to the person skilled in the art. The intermediates described above are commercially available, are known in the art or may be prepared by known procedures.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess 11βHSD1 inhibitory activity. These properties may be assessed using the following assay.

Assay

HeLa cells (human cervical carcinoma derived cells) were stably transfected with a construct containing four copies of the glucocorticoid response element (GRE) linked to a beta-galactosidase reporter gene (3 kb lac Z gene derived from pSV-B-galactosidase). These cells were then further stably transfected with a construct containing full-length human 11βHSD1 enzyme (in pCMVHyg) to create GRE4-βGal/11βHSD1 cells. The principal of the assay is as follows. Cortisone is freely taken up by the cells and is converted to cortisol by 11βHSD1 oxo-reductase activity and cortisol (but not cortisone) binds to and activates the glucocorticoid receptor. Activated glucocorticoid receptor then binds to the GRE and initiates transcription and translation of β-galactosidase. Enzyme activity can then be assayed with high sensitivity by colourimetric assay. Inhibitors of 11βHSD1 will reduce the conversion of cortisone to cortisol and hence decrease the production of β-galactosidase.

Cells were routinely cultured in DMEM (Invitrogen, Paisley, Renfrewshire, UK) containing 10% foetal calf serum (LabTech), 1% glutamine (Invitrogen), 1% penicillin & streptomycin (Invitrogen), 0.5 mg/ml G418 (Invitrogen) & 0.5mg/ml hygromycin (Boehringer). Assay media was phenol red free-DMEM containing 1% glutamine, 1% penicillin & streptomycin.

Compounds (1mM) to be tested were dissolved in dimethyl sulphoxide (DMSO) and serially diluted into assay media containing 10% DMSO. Diluted compounds were then plated into transparent flat-bottomed 384 well plates (Matrix, Hudson NH, USA).

The assay was carried out in 384 well microtitre plate (Matrix) in a total volume of 50μl assay media consisting of cortisone (Sigma, Poole, Dorset, UK, 1μM), HeLa GRE4-βGal/11βHSD1 cells (10,000 cells) plus test compounds (3000 to 0.01 nM). The plates were then incubated in 5% O_2, 95% CO_2 at 37°C overnight.

The following day plates were assayed by measurement of β-galactosidase production.

A cocktail (25μl) consisting of 10X Z-buffer (600 mM Na_2HPO_4, 400 mM $NaH_2PO_4.2H_2O$, 100 mM KCl, 10 mM $MgSO_4.7H_2O$, 500 mM β-mercaptoethanol, pH 7.0), SDS (0.2%), chlorophenol red-β-D-galactopyranoside (5mM, Roche Diagnostics) was added per well and plates incubated at 37°C for 3-4hours. β-Galactosidase activity was indicated by a yellow to red colour change (absorbance at 570nm) measured using a Tecan Spectrafluor Ultra.

The calculation of median inhibitory concentration (IC_{50}) values for the inhibitors was performed using Origin 6.0 (Microcal Software, Northampton MA USA). Dose response

curves for each inhibitor were plotted as OD units at each inhibitor concentration with relation to a maximum signal (cortisone, no compound) and IC_{50} values calculated. Compounds of the present invention typically show an IC_{50} <10μM. For example the following results were obtained:

Example	IC_{50}
380	50nM
13	254nM
223	97nM

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)**, **(If)**, **(Ig)**, Group A or Group C or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.1 – 50 mg/kg that normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective 11βHSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

It is to be understood that where the term "metabolic syndrome" is used herein, this relates to metabolic syndrome as defined in 1) and/or 2) or any other recognised definition of this syndrome. Synonyms for "metabolic syndrome" used in the art include Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X. It is to be understood that where

the term "metabolic syndrome" is used herein it also refers to Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X.

According to a further aspect of the present invention there is provided a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)**, **(If)**, **(Ig)**, Group A or Group C or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is provided a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)**, **(If)**, **(Ig)**, Group A or Group C or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)**, **(If)**, **(Ig)**, Group A or Group C or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound selected from the Reference Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

Where production of or producing an 11βHSD1 inhibitory effect is referred to suitably this refers to the treatment of metabolic syndrome. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly diabetes and obesity. Alternatively, where production of an 11βHSD1 inhibitory effect is referred to this refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man,

in need of such treatment which comprises administering to said animal an effective amount of a compound of Group B or Group C or a compound of formula **(Ih)**, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(Ia)**, **(Ib)**, **(Ic)**, **(Id)**, **(Ie)**, **(If)**, **(Ig)**, Group A or Group C or a pharmaceutically acceptable salt thereof or of the Examples, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound selected from the Reference Examples, or a pharmaceutically acceptable salt thereof.

In addition to their use in therapeutic medicine, the compounds of formula **(I)**, or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of 11βHSD1 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of 11βHSD1 described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with 11βHSD1 inhibitors, particularly those of the present invention, may include the following main categories of treatment:

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
3) Insulin sensitising agents including PPARγ agonists (for example pioglitazone and rosiglitazone);
4) Agents that suppress hepatic glucose output (for example metformin);

5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
6) Agents designed to treat the complications of prolonged hyperglycaemia; e.g. aldose reductase inhibitors
7) Other anti-diabetic agents including phosotyrosine phosphatase inhibitors, glucose 6 - phosphatase inhibitors, glucagon receptor antagonists, glucokinase activators, glycogen phosphorylase inhibitors, fructose 1,6 bisphosphastase inhibitors, glutamine:fructose -6-phosphate amidotransferase inhibitors
8) Anti-obesity agents (for example sibutramine and orlistat);
9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); ileal bile acid absorption inhibitors (IBATi), cholesterol ester transfer protein inhibitors and nicotinic acid and analogues (niacin and slow release formulations);
10) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); calcium antagonists (eg. nifedipine); angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
11) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and
12) Anti-inflammatory agents, such as non-steroidal anti-infammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

<u>Examples</u>

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;

(iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 μm (Merck);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula **(I)** were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated $CDCl_3$ (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C_8(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH^+);

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C_8, 7 μm, (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried sodium sulphate was the drying agent;

(ix) where an "ISOLUTE-Si" column is referred to, this means a column containing 1 or 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE"; "ISOLUTE" is a registered trade mark;

(x) the following abbreviations may be used hereinbefore or hereinafter:-

DCM	dichloromethane;
MeCN	acetonitrile;

THF	tetrahydrofuran;
HATU	O-(7-azabenzotriazol-1-yl)-n,n,n',n'-tetramethyluronium hexafluoro-phosphate;
PS-DIEA	Polymer Supported-Diisopropylethylamine (From Argonaut Technologies);
DIEA	Diisopropylethylamine;
PS-Trisamine	Tris-(2-aminoethyl)amine polystyrene;
LHMDS	Lithium bis(trimethylsilyl)amide;
TFA	trifluoroacetic acid; and
EtOAc	ethyl acetate.

xi) where an Isolute SCX-2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xii) where an Isolute-NH2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of acidic compounds, i.e. a polypropylene tube containing a amino silane covalently bonded to a silica particle used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ;

xiii) where Mettler Toledeo Myriad ALLEX liquid –liquid extractor is referred to this means an automated liquid liquid extraction workstation capable of separating aqueous and organic phases;

xiv) where as Isco CombiFlash Optix-10 parallel flash chromatography system is referred to this means an automated chromatography workstation capable of carrying out up to 10 purifications in parallel via flash chromatography using pre packed silica cartridges;

xv) where a "Biotage Quad3+ flash chromatography system" is referred to this means an automated chromatography workstation capable of carrying out up to 12 purifications in parallel via flash chromatography using pre packed silica cartridges, eg Si 12+M available from Biotage Inc. A Dyax Corp. Company;

xvi) where a "phase separation cartridge" is referred to this is an Isolute Phase Separator (70ml) available from International Sorbent Technology; and

xvii) where a "reverse phase bond elute" is referred to this is a reverse phase bode elute cartridge supplied in various sizes from Varrian.

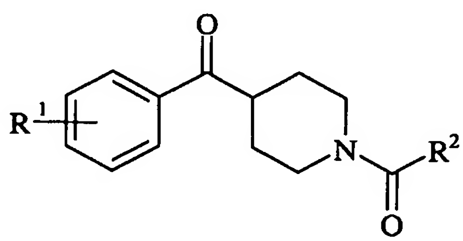
Example 1

1-(4-Fluorobenzoyl)-4-(4-chlorobenzoyl)piperidine

To a stirred solution of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (187mg, 0.72mmol) and triethylamine (240µl, 1.71mmol) in DCM (3ml) was added 4-fluorobenzoyl chloride (109mg, 0.69mmol). The reaction was left to stir at room temperature for one hour then transferred to a sep funnel and diluted to approximately 10ml with DCM. This solution was washed with 2M HCl (5ml), water (5ml) and brine (5ml) then dried, filtered and evaporated to yield product as a solid (70mg, 29%). NMR (DMSO-d_6, 100°C): 1.60 (m, 2H), 1.85 (m, 2H), 3.15 (t, 2H), 3.65 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.55 (d, 2H), 7.95 (d, 2H); m/z: 346.

Examples 2-16 and Reference Examples 1-2

The procedure described in Example 1 was repeated using the appropriate reagent to replace the "4-fluorobenzoyl chloride" and the "(4-chlorophenyl)(4-piperidyl)methanone hydrochloride" to obtain the compounds described below. In some cases a base wash was also carried out ($NaHCO_3$) prior to washing with brine.



Ex	R^1	R^2	NMR	M/z
2	4-Cl	Cyclohexyl	1.25 (br m, 4H), 1.40-2.00 (br m, 10H), 2.50 (m, 1H), 2.80 (br t, 1H), 3.20 (br t, 1H), 3.45 (m, 1H), 4.00 (br m, 1H), 4.60 (br m, 1H), 7.45 (d, 2H), 7.90 (d, 2H)	334
3	4-Cl	4-Methyl-phenyl	0.85 (br m, 1H), 1.25 (s, 1H), 1.80 (m, 4H), 2.35 (s, 3H), 3.10 (br m, 2H), 3.50 (m, 1H), 7.20 (d, 2H), 7.30 (d, 2H), 7.45 (d, 2H), 7.90 (d, 2H)	342
4	4-Cl	fur-2-yl	1.80-2.00 (br m, 4H), 3.20 (br m, 2H), 3.50 (m, 1H), 4.56 (d, 2H), 6.45 (m, 1H), 7.00 (d, 1H), 7.45 (d, 3H), 7.90 (d, 2H)	318

Ex	R^1	R^2	NMR	M/z
5	4-Cl	Cyclopropyl	0.85 (m, 2H), 1.00 (m, 2H), 1.65-2.00 (br m, 5H), 2.90 (br m, 1H), 3.30 (br m, 1H), 3.50 (m, 1H), 4.30 (br s, 1H), 4.55 (br s, 1H), 7.45 (d, 2H), 7.90 (d, 2H)	292
6	4-F	Furan	1.90 (br m, 4H), 3.20 (br m, 2H), 3.50 (m, 1H), 4.50 (d, 2H), 6.50 (m, 1H), 6.95 (d, 1H), 7.15 (t, 2H), 7.50 (s, 1H), 8.00 (m, 2H)	302
7	4-F	Cyclohexyl	1.30 (br m, 3H), 1.40-2.00 (br m, 11H+H20), 2.50 (m, 1H), 2.80 (m, 1H), 3.20 (m, 1H), 3.45 (m, 1H), 4.00 (m, 1H), 4.60 (m, 1H), 7.15 (t, 2H), 7.95 (m, 2H)	318
8	4-F	4-Fluoro-phenyl	1.85 (br s, 4H), 3.10 (br m, 2H), 3.50 (m, 1H), 7.10 (m, 4H), 7.45 (m, 2H), 8.00 (m, 2H)	330
9	4-F	Cyclopropyl	0.75 (m, 2H), 1.00 (m, 2H), 1.75-2.00 (br m, 5H), 2.85 (br m, 1H), 3.30 (br m, 1H), 3.50 (m, 1H), 4.30 (br m, 1H), 4.55 (br m, 1H), 7.10 (t, 2H), 7.95 (m, 2H)	276
RE1	4-Me	Thien-2-yl	DMSO-d_6: 1.50 (m, 2H), 1.85 (m, 2H), 2.35 (s, 3H), 3.20 (m, 2H), 3.75 (m, 1H), 4.30 (br d, 2H), 7.10 (t, 1H), 7.33 (d, 2H), 7.38 (d, 1H), 7.75 (d, 1H), 7.90 (d, 2H)	314
10	4-F	Thien-2-yl	1.55 (m, 2H), 1.85 (m, 2H), 3.20 (m, 2H), 3.80 (m, 1H), 4.30 (br d, 2H), 7.10 (m, 1H), 7.35 (m, 3H), 7.70 (m, 1H), 8.10 (m 2H)	318
11	4-Cl	Thien-2-yl	1.50 (m, 2H), 1.85 (br d, 2H), 3.20 (m, 2H), 3.75 (m, 1H), 4.30 (br d, 2H), 7.10 (m, 1H), 7.35 (d, 1H), 7.60 (d, 2H), 7.75 (d, 1H), 8.00 (d, 2H)	334
RE2	4-Cl	Methyl		266
12	4-OMe	Fur-2-yl	1.85 (m, 4H), 3.10 (br s, 2H), 3.45 (m, 1H), 3.80 (s, 3H), 4.45 (br d, 2H), 6.40 (m, 1H), 6.90 (m, 3H), 7.40 (s, 1H), 7.90 (d, 2H)	314

Ex	R^1	R^2	NMR	M/z
13	4-OMe	4-Fluoro-phenyl		342
14	4-OMe	Cyclopropyl	0.75 (m, 2H), 1.00 (m, 2H), 1.75 (m, 2H), 1.90 (m, 3H), 2.90 (br s, 1H), 3.30 (br s, 1H), 3.50 (m, 1H), 3.85 (s, 3H), 4.30 (br s, 1H), 4.55 (br s, 1H), 6.95 (d, 2H), 7.95 (d, 2H)	288
15 [1]	4-F	4-Fluoro-benzyl	(DMSO-d_6): 1.35 (m, 2H), 1.75 (m, 2H), 2.75 (t, 1H), 3.15 (t, 1H), 3.65 (m, 1H), 3.70 (s, 2H), 4.00 (d, 1H), 4.40 (d, 1H), 7.10 (t, 2H), 7.25 (m, 2H), 7.35 (t, 2H), 8.05 (m, 2H)	344
16	4-Me	4-Fluoro-phenyl	(DMSO-d_6): 1.50 (m, 2H), 1.80 (br s, 2H), 2.35 (s, 3H), 3.10 (br s, 2H), 3.70 (m, 1H), 7.25 (t, 2H), 7.35 (d, 2H), 7.45 (m, 2H), 7.90 (d, 2H)	326

[1] Purified by column chromatography (10g Silica, 40% EtOAc/isohexane)

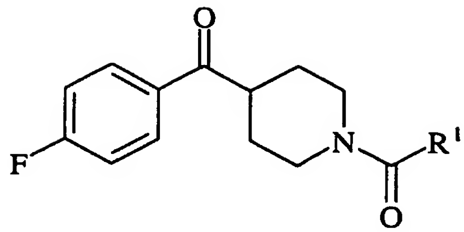
Example 17

1-(5-Chlorothien-2-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 5-chlorothiophene-2-carboxylic acid (35.5mgs, 0.2mmol) in DCM (8 ml) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (57.5mgs, 0.3mmol) and N, N diisopropylethylamine (69.7mgs, 0.5mmol) and the mixture was stirred for 15mins. 4-(4-Fluorobenzoyl)piperidine hydrochloride (58mgs, 0.24mmol) was added and the reaction was stirred for 16hours at room temperature. The solution was washed with 2M HCl (5ml), saturated sodium carbonate (5ml), water (5ml), using a Mettler Toledeo Myriad ALLEX liquid –liquid extractor, then dried, filtered and evaporated to yield the product as a solid (33.6mgs, 43%). M/z 351.

Examples 18-122

The following compounds were prepared by the procedure of Example 17. "*" indicates the carbon atom that is attached to the carbonyl of formula **(A)**.



(A)

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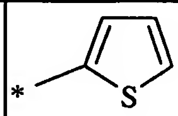
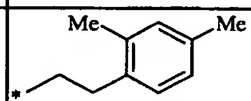
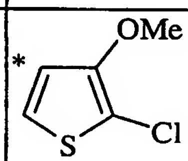
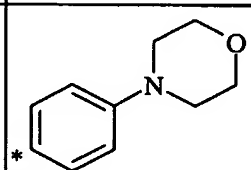
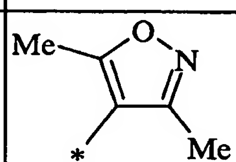
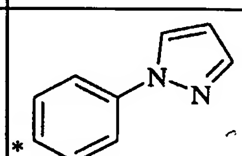
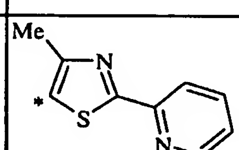
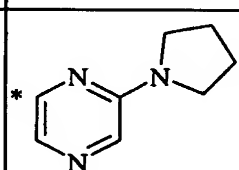
18		331
19		381
20		381
21		396
22		344
23		377
24		409
25		382

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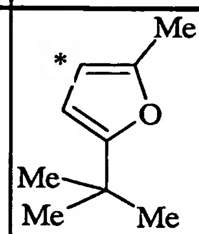
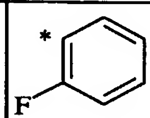
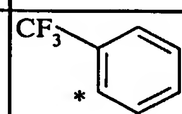
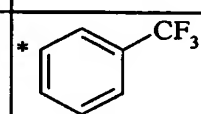
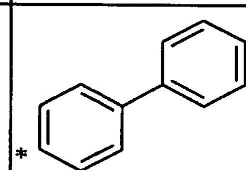
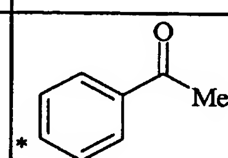
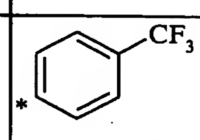
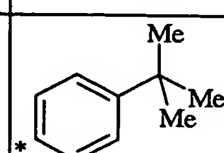
26		371
27		329
28		379
29		379
30		387
31		353
32		379
33		367

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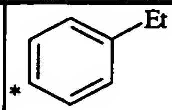
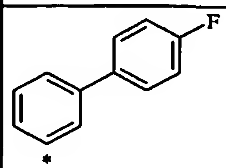
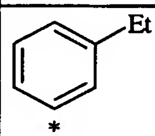
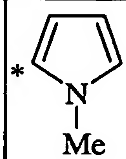
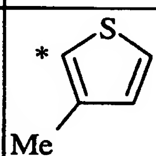
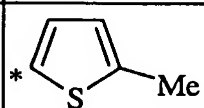
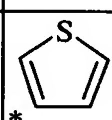
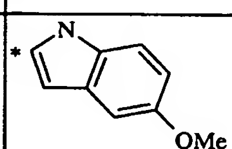
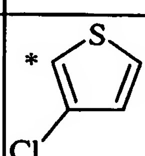
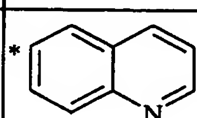
34		339
35		405
36		339
37		314
38		331
39		331
40		317
41		380
42		351
43		362

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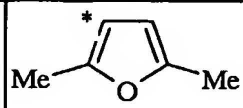
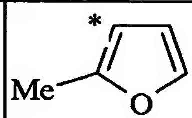
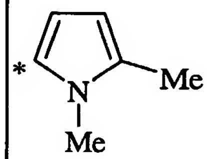
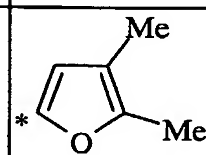
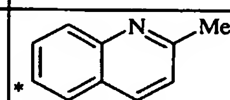
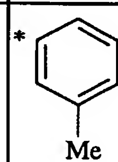
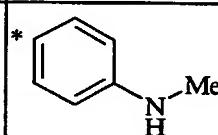
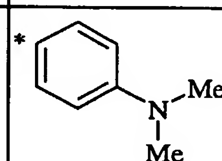
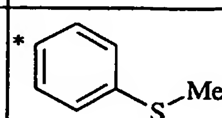
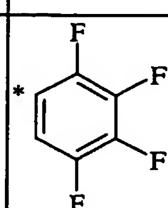
44		329
45		315
46		328
47		329
48		376
49		325
50		340
51		354
52		357
53		383

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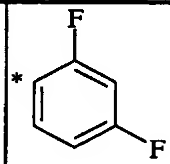
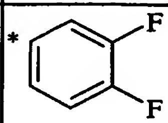
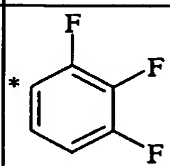
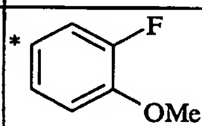
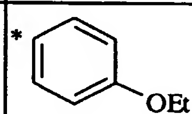
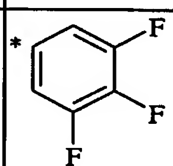
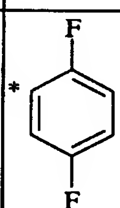
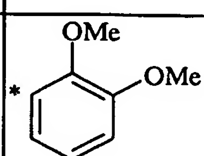
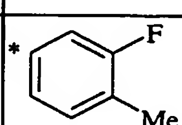
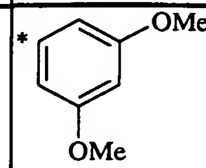
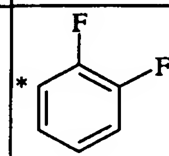
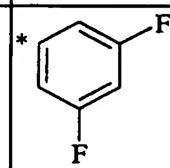
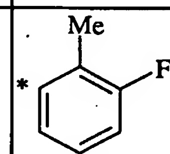
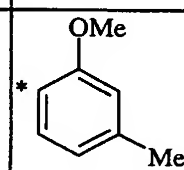
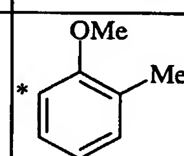
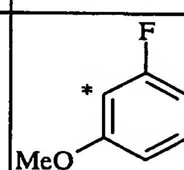
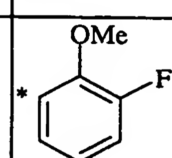
54		347
55		347
56		365
57		359
58		355
59		365
60		347
61		371
62		343
63		371
64		347
65		347
66		343
67		355
68		355
69		359
70		359

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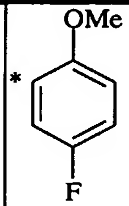
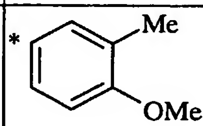
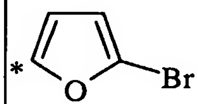
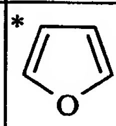
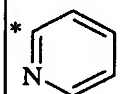
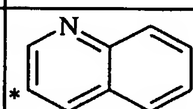
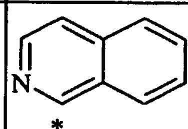
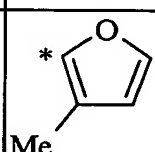
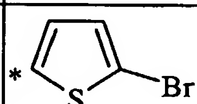
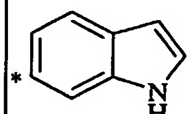
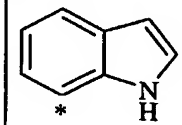
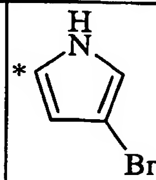
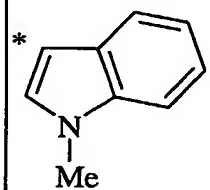
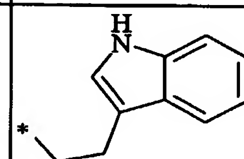
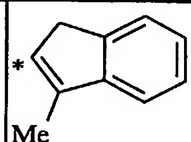
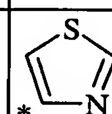
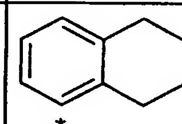
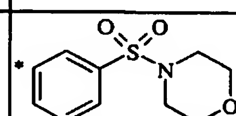
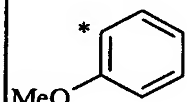
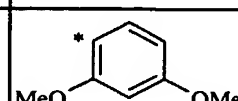
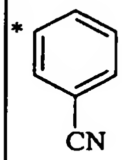
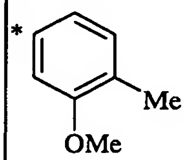
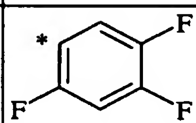
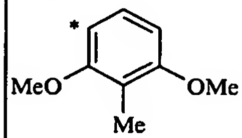
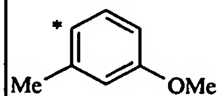
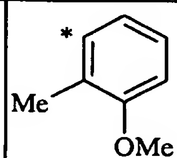
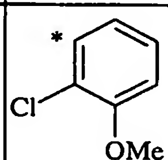
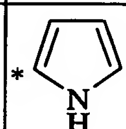
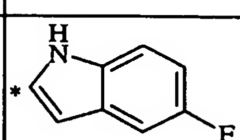
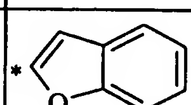
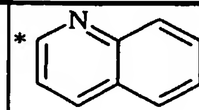
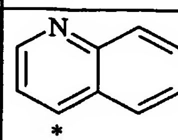
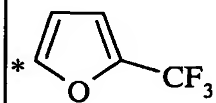
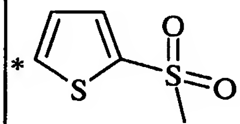
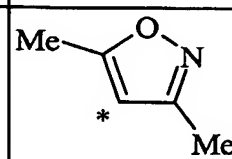
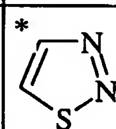
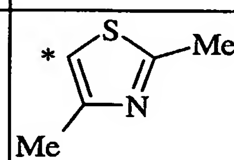
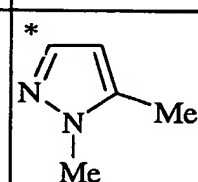
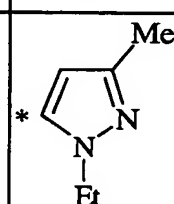
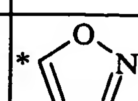
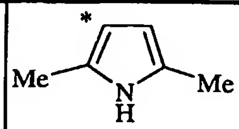
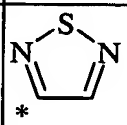
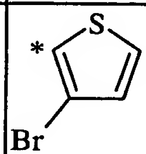
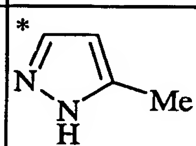
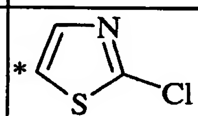
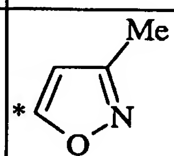
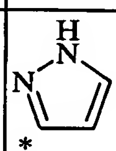
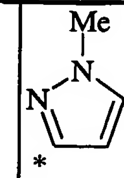
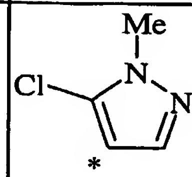
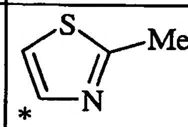
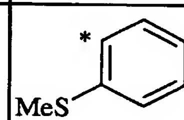
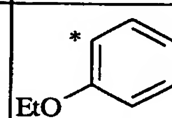
71		359
72		355
73		380
74		301
75		312
76		362
77		362
78		315
79		396
80		350

Ex	R[1]	M/z
81		350
82		379
83		364
84		392
85		363
86		318
87		365
88		460
89		341
90		371

Ex	R^1	M/z
91		336
92		355
93		365
94		385
95		355
96		355
97		376
98		300
99		368
100		351

Ex	R^1	M/z
101		362
102		362
103		369
104		395
105		330
106		319
107		346
108		329
109		343
110		302

Ex	R^1	M/z
111		328
112		319
113		396
114		315
115		353
116		316
117		301
118		315
119		350
120		332
121		357
122		355

Example 123

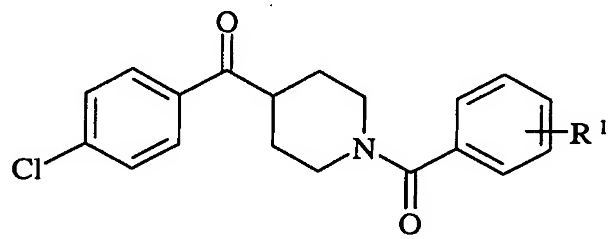
1-(2-Cyanobenzoyl)-4-(4-chlorobenzoyl)piperidine

In a test tube was placed 2-cyanobenzoic acid (49mg, 0.33mmol), 4-(4-chlorobenzoyl)piperidine hydrochloride (86mg, 0.33mmol), N-methylmorpholine (36μl, 0.33mmol) and anhydrous THF (4ml). The resulting suspension was stirred at room temperature for 15minutes before the addition of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride hydrate (106mg, 0.36mmol). The reaction was left to stir overnight at room temperature then worked up. 1M HCl (2ml) was added and the reaction was capped and briefly shaken then allowed to settle. The organic layer was transferred to a 4

dram vial then evaporated to yield crude product. This material was purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN) to yield a solid (19mg, 16%). m/z 353.

Examples 124-129

The procedure described in Example 123was repeated using the appropriate reagent to replace the "2-cyanobenzoic acid" to obtain the compounds described below.



Ex	R^1	M/z
124 [1]	3-MeO	358
125	4- MeO	358
126	3-CN	353
127	2- MeO	358
128	4-CN	353
129	2,4,6-tri MeO	418

[1] NMR: 1.60 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.70 9m, 1H), 3.80 (s, 3H), 4.10 (br s, 2H), 6.95 (m, 2H), 7.00 (d, 1H), 7.35 (t, 1H), 7.60 (d, 2H), 8.00 (d, 2H)

The following General Procedures were used to make Examples 130-345 and Reference Examples 3-5.

General Procedure XX

To the acid (A) in a 2-dram glass vial was added sequentially PS-DIEA (B) and a solution of HATU (C) in DMF (D). The mixture was agitated and allowed to stand for 5-10 minutes prior to the addition of a solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (E) and DIEA (F) in DMF (G). The mixture was shaken, (sonicated if required to effect dissolution) and left to stand, without agitation for 16 h. The reaction mixture was poured onto an Isolute SCX-2 column (1 g, 0.4mmol/g) aligned over an Isolute-NH2 column (1 g, 0.6mmol/g) transferring with DCM (0.5ml). The columns were then eluted under atmospheric pressure with DCM (2.5 column volumes). The eluents were then evaporated *in vacuo*, taken up in MeCN (1ml), an LC-MS analysis sample taken (10µl) and evaporated again *in vacuo* to yield the final compound.

General Procedure YY

To the acid (A) in a 2-dram glass vial was added sequentially: PS-DIEA (B), a solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (E) and DIEA (F) in DMF (G) and a solution of HATU (C) in DMF (D). The mixture was shaken, (sonicated if required to effect dissolution) and left to stand, without agitation for 16 hrs. The reaction mixture was filtered through a double fritted 6ml reservoir, the residue was washed with DCM (0.5ml) and the filtrated was concentrated *in vacuo*. The samples were purified by preparative HPLC. Preparative Reverse Phase HPLC was performed using an Xterra 19x50mm C18 column with a water (A) / MeCN (B) gradient at 25 ml/min as typified in the following table. The eluent was modified during chromatography with a flow of a 5% solution of ammonia in MeCN (C).

Time (mins)	A%	B%	C%
0	94	1	5
1	94	1	5
7.5	0 or 45	95 or 50	5
7.51	0	100	0
8.5	0	100	0
8.51	94	1	5
9.5	94	1	5

General Procedure ZZ

Procedure XX was observed except that the compounds were further dissolved in EtOAc, loaded onto an Isolute-Si 1g column and eluted with EtOAc (3 column volumes). A 15µl analysis sample (for LC-MS) was taken from the filtrate and the remaining evaporated *in vacuo* to provide the desired compounds.

General Procedure AA

Procedure YY was observed except that purification was performed using the Isco CombiFlash Optix-10 parallel flash chromatography system. The evaporated samples were dissolved in EtOAc (1ml) and loaded onto a 2g Isolute-Si column. These were attached to the Optics-10 system over a 12g silica column and run in one of the below methods:

i) Gradient of isohexane/EtOAc, Flow rate 30 ml/min

0 -3 minutes 50% - 100% EtOAc

3-6 minutes 100% EtOAc

ii) Gradient of isohexane/EtOAc, Flow rate 30 ml/min
0 -5 minutes 100% EtOAc

Specific Variations of the above general Procedures are given in the following table

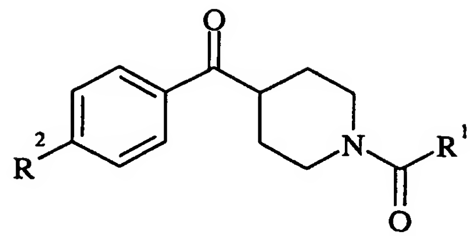
General Procedure	A (mmols)	B (mg) 3.56mmol/g	C (mmol)	D (ml)	E (mmol)	F (mmol)	G (ml)
XXa	0.225	220	0.25	2	0.25	0.5	0.66
XXb	0.225	220	0.25	1.5	0.25	0.25	1
XXc	0.225	220	0.25	1	0.25	0.388	1
XXd	0.225	220	0.25	2	0.25	0.25	0.6
YYa	0.225	220	0.25	1.5	0.25	0.25	1
ZZa	0.225	220	0.25	1	0.25	0.388	1
XXe	0.3	220	0.3	1.5	0.3	0.33	1
YYb	0.3	220	0.3	1.5	0.3	0.33	1
BBg	0.45	220	0.45	1.5	0.45	0.45	1
YYc	0.45	440	0.45	1	0.5	0.657	1
XXf	0.225	220	0.225	1	0.225	0.338	1
XXh	0.3	260	0.3	1	0.3	0.45	1
ZZh	0.3	260	0.3	1	0.3	0.45	1
YYf	0.225	220	0.225	1	0.225	0.338	1
BBf	0.225	220	0.225	1	0.225	0.338	1
YYh	0.3	260	0.3	1	0.3	0.45	1

General Procedure BB

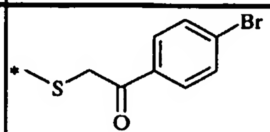
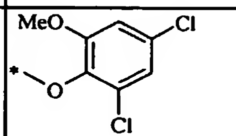
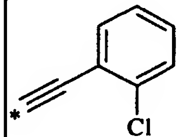
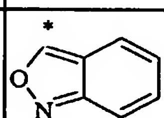
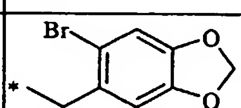
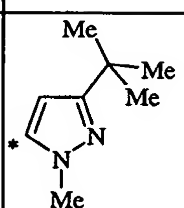
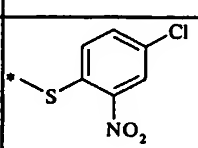
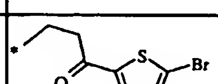
Procedure YY was observed except that purification was performed using a Biotage Quad3+ flash chromatography system. The evaporated samples were dissolved in DCM (1ml) and loaded onto Biotage Si 12+M columns, which were placed in the Biotage system and chromatographed using either isohexane (25%)/EtOAc (75%) or isohexane (50%)/EtOAc (50%) depending on the polarity of the compound.

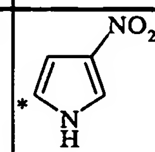
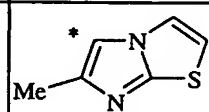
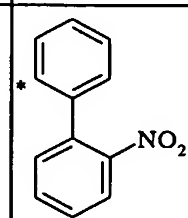
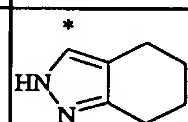
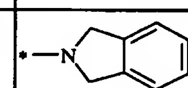
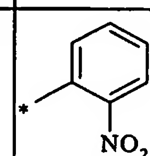
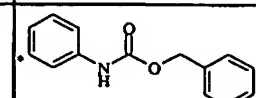
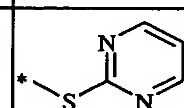
Examples 130-345 and Reference Examples 3-5

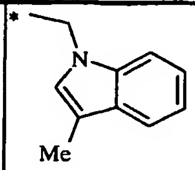
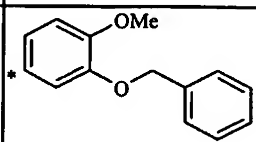
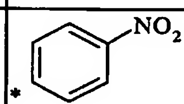
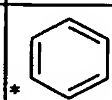
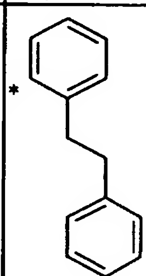
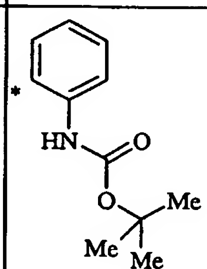
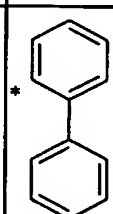
The following compounds were prepared by the General Procedures detailed above. "*" indicates the carbon atom that is attached to the carbonyl of formula (A).

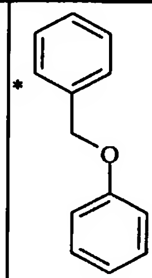
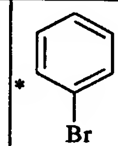
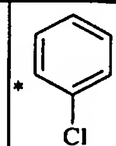
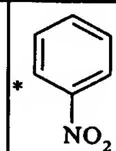
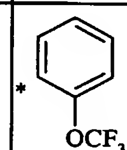
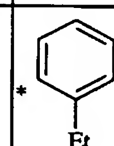
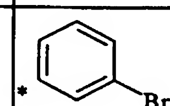
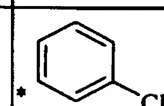
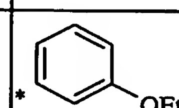


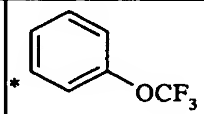
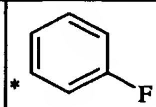
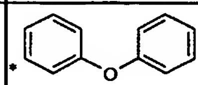
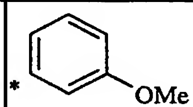
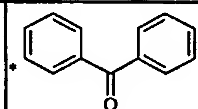
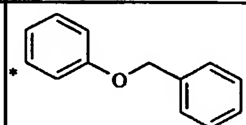
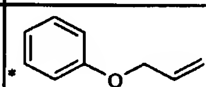
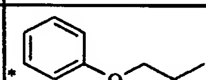
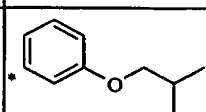
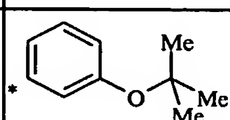
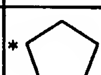
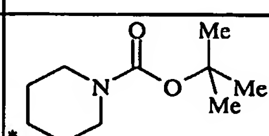
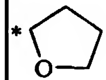
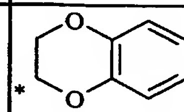
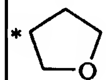
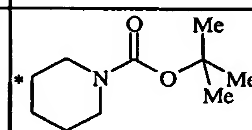
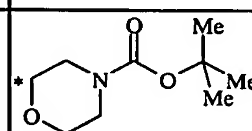
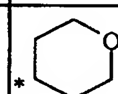
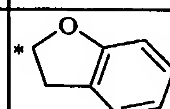
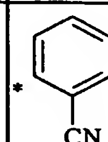
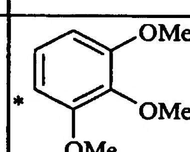
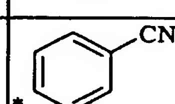
(A)

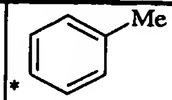
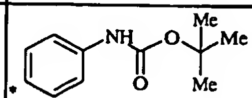
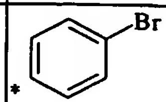
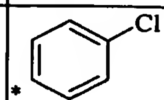
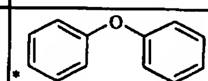
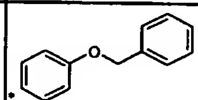
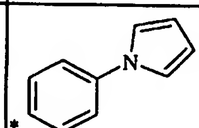
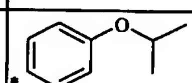
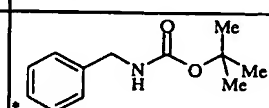
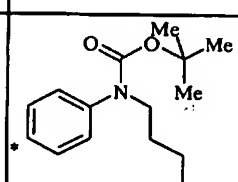
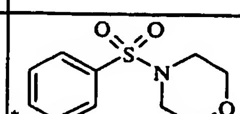
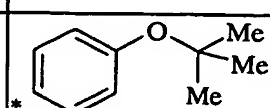
Ex	G. Proc	R^1	R^2	M/z
130	XXb		F	480.3
131	XXb		F	440.3
132	XXa		F	370.4
133	XXa		F	353.4
134	XXa		F	464.3
135	YYa		F	372.7
136	XXb		F	437.3
137	XXb		F	468.3

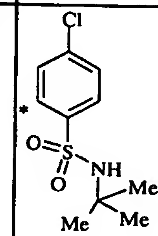
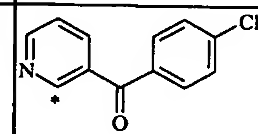
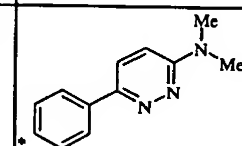
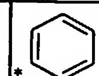
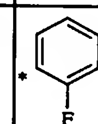
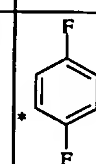
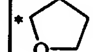
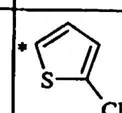
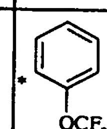
Ex	G. Proc	R^1	R^2	M/z
138	YYa		F	346.7
139	YYa		F	372.7
140	YYa		F	432.5
141	YYa		F	355
142	YYa		F	367.7
143	XXa		F	371.4
144	XXa		F	461.4
145	YYa		F	359

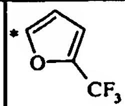
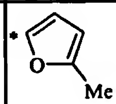
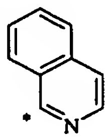
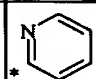
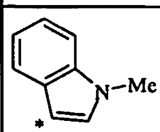
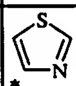
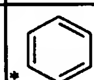
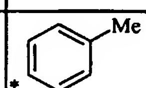
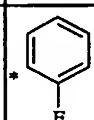
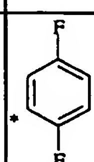
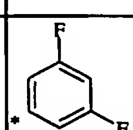
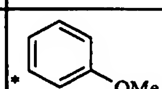
Ex	G. Proc	R^1	R^2	M/z
146	YYa		F	393.7
147	XXa		F	448.4
RE3[1]	XXd		F	357.36
148	XXc		F	312.45
149	XXc		F	416.48
150	XXc		F	427.46
151	XXc		F	388.47

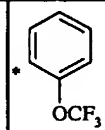
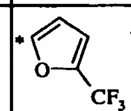
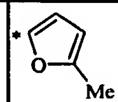
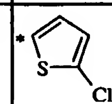
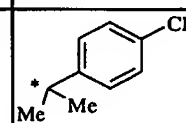
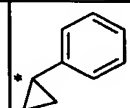
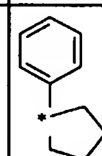
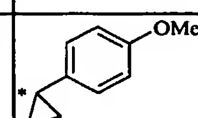
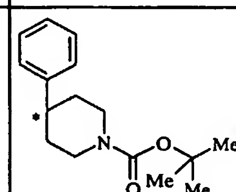
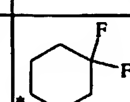
Ex	G. Proc	R^1	R^2	M/z
152	XXc		F	418.45
153	XXc		F	390.35
154	XXc		F	346.42
155	XXc		F	347.45
156	XXc		F	396.42
157	XXc		F	340.5
158	ZZa		F	390.2
159	ZZa		F	346.3
160	ZZa		F	356.4

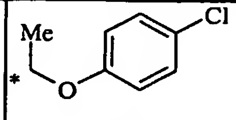
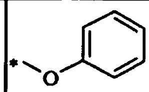
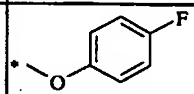
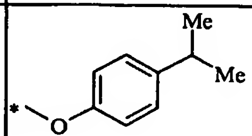
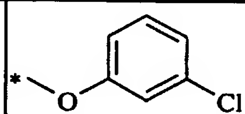
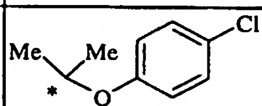
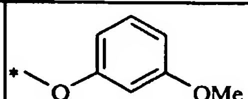
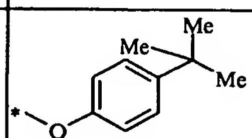
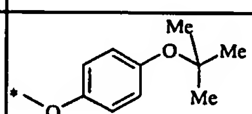
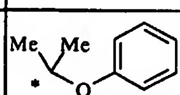
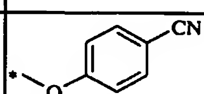
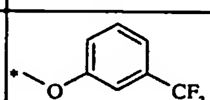
Ex	G. Proc	R^1	R^2	M/z
161	ZZa		F	396.3
162	ZZa		F	330.4
163	ZZa		F	404.3
164	ZZa		F	342.4
165	ZZa		F	416.3
166	ZZa		F	418.3
167	ZZa		F	368.4
168	ZZa		F	370.4
169	ZZa		F	384.4
170	ZZa		F	384.4
171	XXc		F	304.52
172	XXc		F	419.55
173	XXc	*i*-Pr	F	278.51
174	XXc	Hept-3-yl	F	334.4
175	XXc	*t*-Butyl	F	292.4
176	XXc		F	306.51
177	XXc		F	370.52
178	XXc	Pent-3-yl	F	306.55
179	XXc		F	306.52
180	XXc		F	419.57
181	XXc		F	421.54
182	XXc		F	320.54
183	XXc		F	354.55
184	XXc		F	337.45
185	XXc		F	402.54
186	ZZa		F	337.3

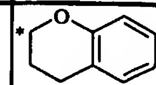
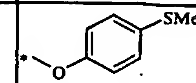
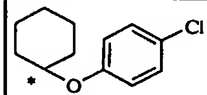
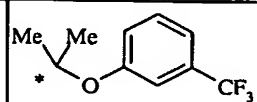
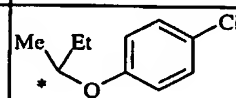
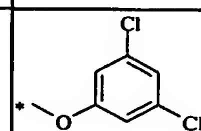
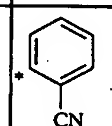
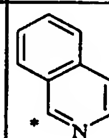
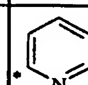
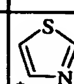
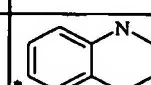
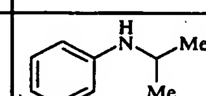
Ex	G. Proc	R¹	R²	M/z
187	ZZa		F	326.3
188	ZZa		F	427.3
189	ZZa		F	390.2
190	ZZa		F	346.3
191	ZZa		F	404.3
192	ZZa		F	418.3
193	ZZa		F	377.3
194	ZZa		F	370.4
195	ZZa		F	441.3
196	ZZa		F	427.3
197	ZZa		F	461.3
198	ZZa		F	384.4

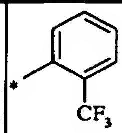
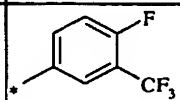
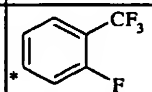
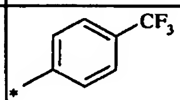
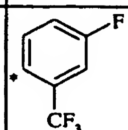
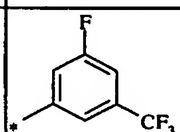
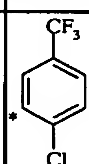
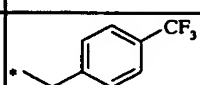
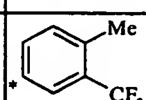
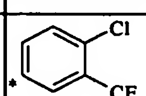
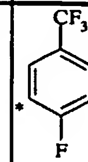
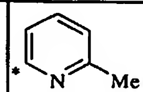
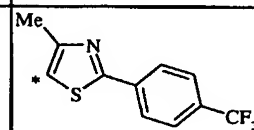
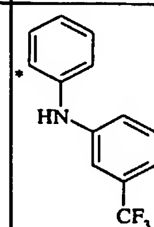
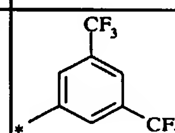
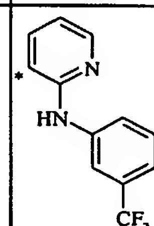
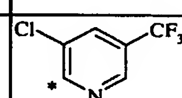
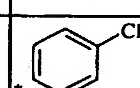
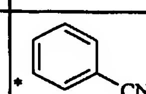
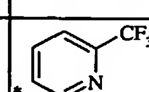
Ex	G. Proc	R¹	R²	M/z
199	XXb	*CH_2-S-C(S)-NMe_2	F	369.4
200	XXb		F	479.4
201	YYa		F	451.5
202	YYa		F	433.6
203	XXe		Cl	328.5
204	XXe		Cl	346.4
205	XXe		Cl	364.4
206	XXe		Cl	322.5
207	XXe	Pent-3-yl	Cl	322.5
208	XXe		Cl	368.4
209	XXe		Cl	412.4

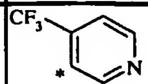
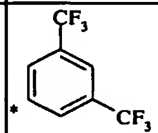
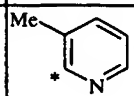
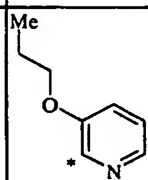
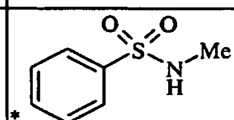
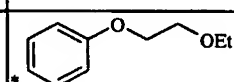
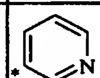
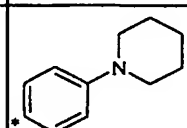
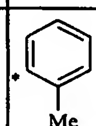
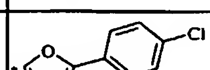
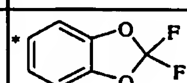
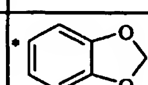
Ex	G. Proc	R^1	R^2	M/z
210	XXe		Cl	386.4
211	XXe		Cl	332.4
212	YYb		Cl	379.5
213	YYb		Cl	329.4
214	YYb		Cl	381.5
215	YYb		Cl	335.4
216	YYb		MeO	324.5
217	XXe		MeO	338.5
218	XXe		MeO	342.5
219	XXe		MeO	360.5
220	XXe		MeO	360.5
221	XXe		MeO	354.5

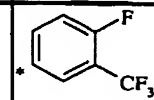
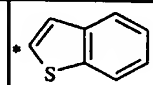
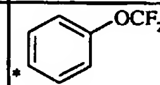
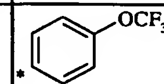
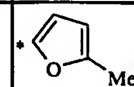
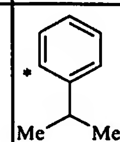
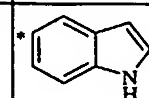
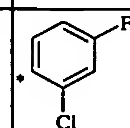
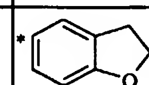
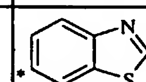
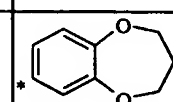
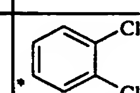
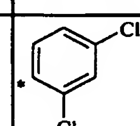
Ex	G. Proc	R^1	R^2	M/z
222	XXe	Pent-3-yl	MeO	318.5
223	XXe		MeO	408.5
224	XXe		MeO	382.4
225	XXe		MeO	328.5
226	XXe		MeO	364.4
227	XXe		F	388.4
228	XXe		F	352.5
229	XXe		F	380.5
230	XXe		F	382.5
231	XXe		F	439.5 (M - *t*-butyl)
232	XXe		F	354.5
233	XXe	*CH_2-CF_3	F	318.4

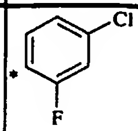
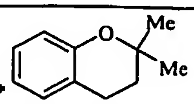
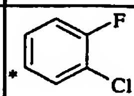
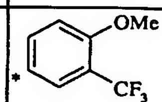
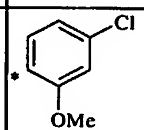
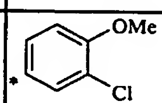
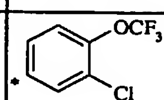
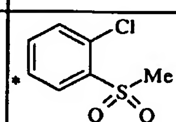
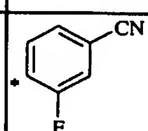
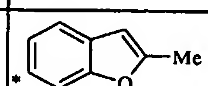
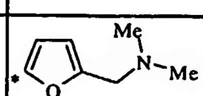
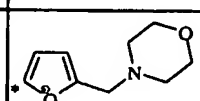
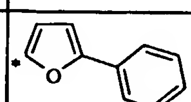
Ex	G. Proc	R[1]	R[2]	M/z
234	XXe		F	390.4
235	ZZe		F	342.5
236	XXe		F	360.5
237	XXe		F	384.5
238	ZZe		F	376.4
239	XXe		F	404.4
240	XXe		F	372.5
241	ZZe		F	398.5
242	ZZe		F	414.5
243	XXe		F	370.5
244	ZZe		F	367.5
245	ZZe		F	410.4

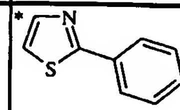
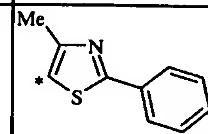
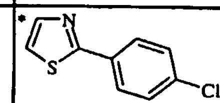
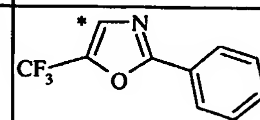
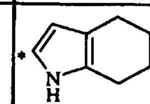
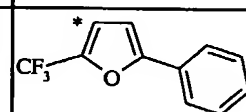
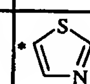
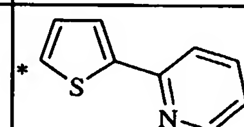
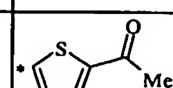
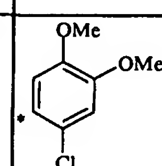
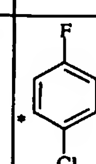
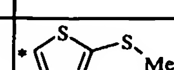
Ex	G. Proc	R[1]	R[2]	M/z
246	ZZe		F	368.5
247	ZZe		F	388.5
248	XXe		F	444.4
249	XXe		F	438.4
250	ZZe		F	418.4
251	XXe		F	410.5
252	XXe		MeO	349.5
253	YYb		MeO	375.5
254	YYb		MeO	325.5
255	YYb		MeO	331.5
256	BBg		F	367.5
257	BBg		F	369.5

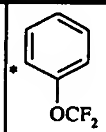
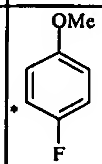
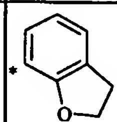
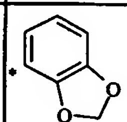
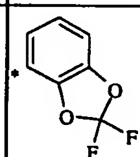
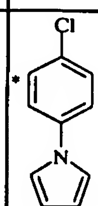
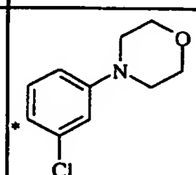
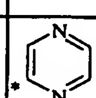
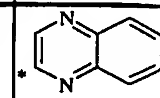
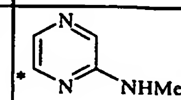
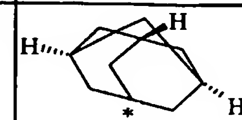
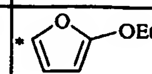
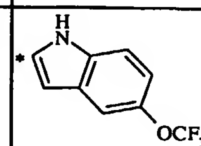
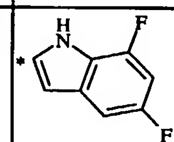
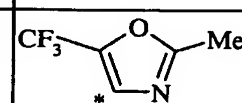
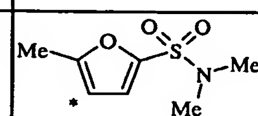
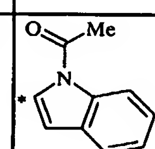
Ex	G. Proc	R^1	R^2	M/z
258	XXe		F	394.4
259	XXe		F	412.5
260	XXe		F	398.4
261	XXe		F	394.5
262	XXe		F	398.5
263	XXe		F	412.5
264	XXe	*$(CH_2)_2CF_3$	F	332.5
265	XXe		F	414.4
266	XXe		F	408.5
267	XXe		F	394.5
268	XXe	*CH(Me)-CH_2-CF_3	F	346.5
269	XXe		F	414.4
270	XXe		F	398.4
271	YYb		F	327.5
272	YYb		F	477.6
273	YYb		F	471.6
274	YYb		F	462.6
275	YYb		F	472.6
276	YYb		F	415.4
277	YYb		Cl	362.4
278	XXe		MeO	349.5
279	YYb		F	381.5

Ex	G. Proc	R¹	R²	M/z
280	YYb		F	381.5
281	XXe		F	448.4
282	YYb		F	327.5
283	YYb		F	371.6
284	ZZa		F	405.3
285	ZZa		F	400.4
RE4	YYc		F	313.5
286	YYc		F	395.5
287	XXf		F	326.5
288	XXf		F	412.4
289	XXf		F	392.4
290	XXf		F	356.5

Ex	G. Proc	R¹	R²	M/z
291	XXf		F	398.4
292	XXf		F	368.4
293	XXf		F	378.5
294	XXf		F	396.4
295	XXf		F	316.5
296	XXf		F	354.5
RE5	XXh		F	351.5
297	XXh		F	364.4
298	XXh		F	354.5
299	XXh		F	369.4
300	XXh		F	384.5
301	XXh		F	380.4
302	XXh		F	380.4

Ex	G. Proc	R^1	R^2	M/z
303	XXh		F	364.4
304	ZZh		F	396.5
305	XXh		F	364.4
306	XXh		F	410.5
307	XXh		F	376.5
308	XXh		F	376.5
309	XXh		F	430.4
310	XXh		F	424.4
311	XXh		F	355.5
312	XXh		F	366.5
313	YYf		F	359.1
314	YYf		F	401.5
315	BBf		F	378.4

Ex	G. Proc	R^1	R^2	M/z
316	YYg		F	395.7
317	YYg		F	409.8
318	YYg		F	429.7
319	YYg		F	447.8
320	YYg		F	355.8
321	YYg		F	446.7
322	YYg		F	319.7
323	XXh		F	395.5
324	XXh		F	360.5
325	XXh		F	406.5
326	XXh		F	364.5
327	XXh		F	364.5

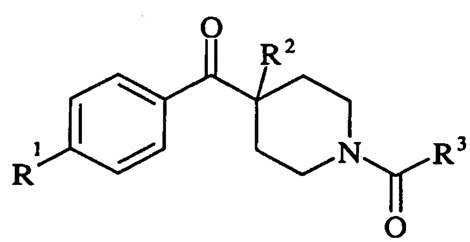
Ex	G. Proc	R^1	R^2	M/z
328	XXh		F	378.5
329	XXh		F	360.5
330	XXh		F	354.6
331	XXh		F	356.5
332	XXh		F	392.5
333	XXh		F	411.5
334	XXh		F	431.5
335	YYg	*CH_2-N(Me)-C(O)-O-*t*-Bu	F	279.7 (M - Boc)
336	YYg		F	314.7
337	YYg		F	364.7
338	YYg		F	343.8
339	XXh		F	370.6
340	XXh		F	346.5
341	YYg		F	435.7
342	YYg		F	387.7
343	YYg		F	385.7
344	YYg		F	423.7
345	YYg		F	393.7

[1] NMR (300MHz) 1.8-2.2 (4H), 3.0-3.4 (2H), 3.4-4.0 (2H), 4.5-4.8 (1H), 7.2 (2H), 7.6 (2H), 8.0 (2H), 8.4 (2H).

Examples 346-351

The following general procedure was used to make Examples 346-351.

To the Acid, R3-C(O)-OH, (1.83 mmol) in a 4-dram glass vial was added sequentially PS-DIEA (880mg) and a solution of HATU (1.83 mmol) in DMF (6ml). The mixture was agitated and allowed to stand for 5-10 minutes prior to the addition of a solution of benzoyl piperidine, (R1-Ph C(O)-piperidine), (1.83 mmol) and DIEA (2.01 mmol) in DMF (6ml). The mixture was shaken, (sonicated if required to effect dissolution) and left to stand, without agitation for 16 hours. The reaction mixture was poured onto an Isolute SCX-2 column (10g) transferred with DCM (2ml) and eluted with DCM (2.5 column volumes), the filtrate was then passed through and Isolute-NH2 column (20g) and eluted with DCM. The eluents were then evaporated *in vacuo* taken up in EtOAc and evaporated again *in vacuo* to give the piperidine amide. The amides (0.29 mmol) were dissolved in THF (2.5 ml) and LHMDS (0.46 ml of a 1.6 M solution in THF) added, alkylating agent (R^2-Br) (1.18mmol) was then added. The reactions were stirred at room temperature, under argon for 19 hours and then quenched with water. The reactions mixtures were concentrated *in vacuo*, diluted with DCM and passed through a phase separation cartridge. The crude materials were purified using a Biotage Quad3+ flash chromatography system eluting with 25% EtOAc/isohexane to afford the final compounds.



Ex	R^1	R^2	R^3	NMR	M/z
346	F	Me	4-Cl-phenyl	7.81 (2H, dd), 7.38 (2H, d), 7.30 (2H, d), 7.12 (2H, dd), 4.10 (1H, bs), 3.23-3.11 (2H, m), 2.34 (2H, bs), 2.82-1.34 (2H, m), 1.49 (3H, s)	360.4
347	F	Me	cyclopentyl	7.80 (2H, dd), 7.28 (2H, dd), 3.60 (1H, bs), 3.30 (3H, s), 3.25 (1H, m), 3.12 (1H, m), 2.93 (1H, m), 2.10 (2H, bs), 1.8-1.45 (10 H, m), 1.40 (3H, s)	318.5

Ex	R^1	R^2	R^3	NMR	M/z
348	F	Et	cyclopentyl	7.80 (2H, dd), 7.10 (2H, dd), 4.15 (1H, bd), 3.71 (1H, bd), 3.18 (1H, td), 2.70-2.2.90 (2H, m), 2.38 (1H, bd), 2.25 (1H, bd), 1.99 (1H, m), 1.90-1.60 (9H m), 1.60-1.49 (3H, m), 0.89 (3H, t)	332.6
349	Cl	Me	cyclopentyl	7.69 (2H, d), 7.38 (2H, d), 3.92 (1H, bs), 3.70-3.59 (2H, m), 3.29 (1H, bs), 3.05 (1H, bs), 2.89 (1H, m), 2.23 (2H, bs), 1.90-1.67 (6H, m), 1.67-1.49 (4H, m), 1.45 (3H, s)	334.5
350	Cl	Pr	cyclopentyl	7.68 (2H, d), 7.38 (2H, d), 4.17 (1H, bs), 3.70 (1H, bs), 3.15 (1H, bs), 2.91-2.72 (3H, m), 2.40 (1H, bd), 2.27 (1H, bd), 1.92-1.61 (9H, m), 1.60-1.40 (5H, m)	362.6
351	Cl	Et	cyclopentyl	7.69 (2H, d), 7.40 (2H, d), 4.15 (1H, bd), 3.71 (1H, bd), 3.14 (1H, dd), 2.90-2.71 (2H, m), 2.42 (1H, bd), 2.31 (1H, bd), 2.00 (1H, m), 1.90-1.67 (7H, m), 1.58 (2H, m), 1.45 (1H, dd), 0.85 (3H, t)	348.5

<u>Examples 352 -353</u>

The following general procedure was used to make Examples 352-353.

The relevant Boc protected amides (10 mg) were taken up in 1,4-dioxane (1ml) and 4M HCl was added (1ml). The reactions were allowed to stand at room temperature for 24 hours. The reaction mixes were then concentrated *in vacuo* to afford the corresponding hydrochloride salts.

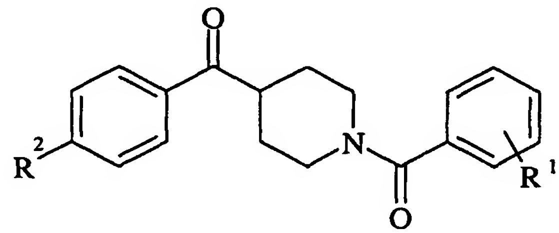
Ex	Compound	M/z	SM
352	1-[4-(*N*-butylamino)benzoyl]-4-(4-fluorobenzoyl)piperidine	383.5	Ex 196
353	1-(2-aminobenzoyl)-4-(4-fluorobenzoyl)piperidine	327.5	Ex 150

<u>Examples 354-356 and Reference Example 6</u>

The following general procedure was used to make Examples 354-356 and Reference Example 6.

To a solution of the acid (0.3mmol) in DMF (1ml) was added sequentially PS-DIEA (190mg @ 3.56mmol/g) and a solution of HATU (0.3mmol) in DMF (1ml). The mixture was allowed to stand for 5-10 minutes prior to the addition of a solution of amine (0.3mmol) and

DIEA (0.3mmol) in DMF (1ml). The mixture was shaken for 2 hours, then allowed to stand for 16 hours. The reaction mixture was filtered to remove PS-DIEA. The reaction mixture was poured onto an Isolute SCX-2 column (1g, 0.4mmol/g) aligned over an Isolute-NH_2 (1g, 0.6mmol/g) transferring with DCM (0.5ml). The columns were then eluted under atmospheric pressure with DCM (2.5 column volumes). An LCMS sample was taken, then the eluents were evaporated in vacuo to yield the final compound.



Ex	R^1	R^2	M/z
RE6	H	H	294
354	4-*i*-PrO	Cl	368
355	2-CN	H	317
356	2-CF_3O	H	378

Example 357

1-(4-Methoxybenzoyl)-4-(4-fluorobenzoyl)piperidine

To paramethoxy benzoic acid (34mg, 0.225mmol) in a 2-dram glass vial was added a suspension of 4-(4-fluorobenzoyl)piperidine hydrochloride (0.25mmol (60mg), HATU (0.25mmol, 95mg) and DIEA (0.75mmol, 130μl) in THF (2ml), transferring with a further 1 ml of THF. The mixture was stirred for 19h, filtered over Isolute SCX-2 (2x2g) washing through with THF (1 column volume). The filtrate in turn was filtered over Isolute-NH2 (1g) washing with THF (1 column volume). The filtrates were evaporated in vacuo to result a colourless oil. Dissolution and evaporation from methanol yielded a white solid. Yield 64.6mg, 76.8%. NMR (300MHz) 1.8-2.0 (4H), 3.0-3.2 (2H), 3.4-3.6 (1H), 3.9 (3H), 4-4.6 (2H), 6.9 (2H), 7.2 (2H), 7.4 (2H), 8.0 (2H); m/z 342.47.

Example 358

4-(4-Trifluoromethoxybenzoyl)piperidine hydrochloride

To a suspension of Rieke Magnesium (101mg, 4.15mmols) in anhydrous THF (8ml) was added a solution of 1-bromo-4-(trifluoromethoxy)benzene in anhydrous THF (4ml). The

reaction was left to stand for 5 minutes then stirred for a further 5 minutes. To the resulting solution was added a solution of 1-(*t*-butoxycarbonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (J. Med. Chem. 2000, 43, 21, 3895-3905; 282mg, 1.04mmols) in anhydrous THF (4ml). The resulting reaction was stirred at room temperature for 30 minutes then quenched with sat NH_4Cl solution (20ml). The reaction mixture was partitioned between water (20ml) and EtOAc (20ml), the layers were separated and the aqueous layer was reextracted with EtOAc (10ml). The combined organics were washed with brine (10ml) and dried ($MgSO_4$), filtered and evaporated to yield a solid. This solid was dissolved in DCM (10ml) and treated with TFA (1.5ml), the resulting reaction was stirred at room temperature for 1 hour then diluted to ~20ml and washed with 1M NaOH (20ml) and brine (10ml). The DCM was evaporated under reduced pressure to yield an orange oil. This oil was loaded onto an Isolute SCX-2 column which was then flushed through with MeOH, when all impurities had eluted the product was eluted off with 1% NH_3/MeOH solution. The product was dissolved in EtOH (20ml) and treated with 1.1eq of 1M HCl in ether. The solvent was then evaporated to yield the title compound (80mg, 25%). M/z 274.

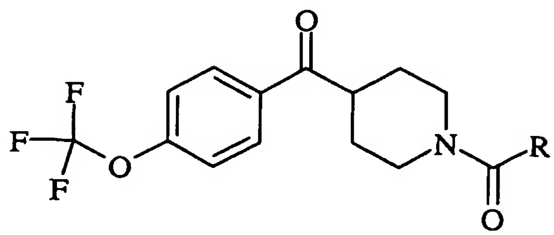
Example 359

1-(Cyclohexylcarbonyl)-4-(4-trifluoromethoxybenzoyl)piperidine

To a stirred solution of 4-(4-trifluoromethoxybenzoyl)piperidine hydrochloride Example 358; 100mg, 0.32mmols) and triethylamine (82mg, 0.81mmols) in DCM (5ml) was added cyclohexanecarbonyl chloride (43mg, 0.29mmols). The reaction was stirred at room temperature for 3 hours before washing with 1M HCl (2 x 3ml), sat $NaHCO_3$ (3ml) and brine. The resulting solution was then evaporated to yield the product (28mg, 25%). M/z 384.

Examples 360-362

The procedure described in Example 359 was repeated using the appropriate reagent to replace the "cyclohexanecarbonyl chloride" to obtain the compounds described below. The products were additionally purified by column chromatography (10g Silica, 20 to 60% EtOAc/isohexane).



Ex	R	NMR	M/z
360	Ph	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.15 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.35 (m, 2H), 7.45 (m, 5H), 8.10 (d, 2H)	378
361	4-CN Ph	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.15 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.45 (d, 2H), 7.55 (d, 2H), 7.85 (d, 2H), 8.10 (d, 2H)	403
362	4-Cl Ph	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.15 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.40 (d, 2H), 7.45 (m, 4H), 8.10 (d, 2H)	412

Example 363

1-(2-Fluoro-5-methylbenzoyl)-4-(4-fluorobenzoyl)piperidine

The title compound was prepared by the procedure of Example 17. M/z 344.

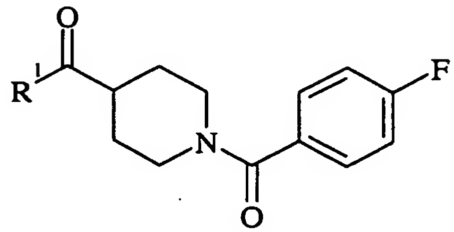
Example 364

1-(4-Fluorobenzoyl)-4-(3-chlorobenzoyl)piperidine

To a stirred solution of 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 327mg, 1.11mmol) in anhydrous THF (8ml) at 0°C was added a 0.5M solution of 3-chlorophenyl magnesium bromide in THF (6.66ml, 3.33mmol). The reaction was stirred at 0°C for ten minutes then allowed to warm to room temperature and stirred for a further 30 minutes. The reaction was quenched with sat NH_4Cl (~20ml) and extracted with EtOAc (2 x 15ml). The combined organic layers were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 20% EtOAc/isohexane to 40%EtOAc/isohexane) to yield a solid (55mg, 15%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.40 (m, 2H), 7.50 (t, 1H), 7.65 (m, 1H), 7.90 (m, 2H); m/z 346.

Examples 365-376

The procedure described in Example 364was repeated using the appropriate reagent to replace the "3-chlorophenyl magnesium bromide" to obtain the compounds described below.



Ex	R¹	NMR	M/z
365	Benzyl	NMR (DMSO-d_6): 1.45 (m, 2H), 1.85 (br s, 2H), 2.80 (m, 1H), 2.95 (br s, 2H), 3.85 (s, 2H), 7.15 (d, 2H), 7.30 (m, 5H), 7.45 (m, 2H)	326
366	4-Propyl-phenyl	NMR (DMSO-d_6): 0.90 (t, 3H), 1.60 (m, 4H), 1.85 (m, 2H), 2.65 (t, 2H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 3H), 7.40 (d, 2H), 7.45 (m, 2H), 7.90 (d, 2H)	354
367	2-Chloro-thien-5-yl	NMR (DMSO-d_6): 1.65 (m, 2H), 1.85 (m, 2H), 2.20 (t, 2H), 3.55 (m, 1H), 4.05 (m, 2H), 7.20 (m, 3H), 7.45 (m, 2H), 7.90 (d, 1H)	352
368	2-Methyl-pyrid-6-yl		327
369	3-Methyl-phenyl	1.60 (m, 2H), 1.85 (br d, 2H), 2.40 (s, 3H), 3.20 (t, 2H), 3.70 (m, 1H), 4.00 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 4H), 7.80 (m, 2H)	326
370	4-*t*-Butyl-Phenyl	1.30 (s, 9H), 1.60 (m, 2H), 1.80 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.55 (d, 2H), 7.90 (d, 2H)	368
371	3-Methoxy-phenyl	1.65 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 3.85 (s, 3H), 4.05 (m, 2H), 7.25 (m, 3H), 7.45 (m, 4H), 7.60 (d, 1H)	342
372	4-Phenyl-phenyl	1.60 (m, 2H), 1.90 (m, 2H), 3.20 (t, 2H), 3.75 (m, 1H), 4.05 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 5H), 7.70 (d, 2H), 7.80 (d, 2H), 8.05 (d, 2H)	388
373	Cyclopentyl		304

Ex	R[1]	NMR	M/z
374	1,3-Benzodioxol-5-yl		356
375[3]	2-Methyl phenyl		326
376	4-MeS phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 2.55 (s, 3H), 3.20 (m, 2H), 3.65 (m, 1H), 4.00 (br d, 2H), 7.25 (t, 2H), 7.40 (d, 2H), 7.45 (d, 2H), 7.90 (d, 2H)	358

[1] Further purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN)

[2] Further purified by prep LCMS (9-95% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN)

[3] Further purified by prep LCMS, conditions in the following table where A is water; B is MeCN; and C is 36% ammonia / MeCN. Collection was at 254 nm.

Time (mins)	A%	B%	C%
0	94	1	5
1	94	1	5
7.5	0	95	5
7.51	0	100	0
8.5	0	100	0
8.51	94	1	5
9.5	94	1	5

Example 377

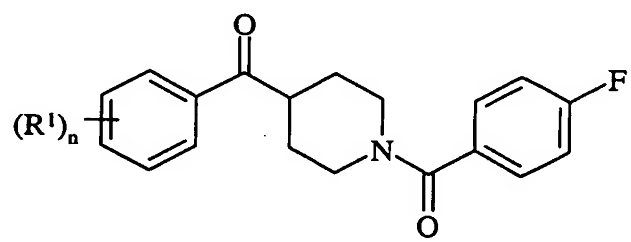
1-(4-Fluorobenzoyl)-4-(3-methoxymethylbenzoyl)piperidine

To a suspension of Rieke Mg (36mg) in THF (1.4ml) at room temperature, under Argon, was added a solution of (3-bromophenyl) methyl methyl ether (JACS, 1989, 111(16), 6311-20; 301mg, 1.5mmol). The reaction was left to stand for 10 minutes then stirred slowly for a further 5 minutes. To the resulting yellow solution was added a solution of 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 150mg, 0.51mmol) in THF (1ml). The reaction was stirred at room temperature for 3.5 hours then quenched with sat NH_4Cl (~10ml) and extracted with EtOAc (2x5ml). The combined organics were washed

with brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (20g Silica, 20 to 60% EA/isohexane) to yield the product as a white solid (40mg, 30%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 3.20 (t, 2H), 3.35 (s, 3H), 3.70 (m, 1H), 4.00 (m, 2H), 4.50 (s, 2H), 7.20 (t, 2H), 7.50 (br m, 3H), 7.55 (d, 1H), 7.90 (s, 2H); m/z 356.

Examples 378-392

The procedure described in Example 377 was repeated using the appropriate reagent to replace the "(3-Bromophenyl) methyl methyl ether" to obtain the compounds described below.



Ex	$(R^1)_n$	NMR	M/z
378	4-CF_3	NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.75 (m, 1H), 4.00 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.85 (d, 2H), 8.15 (d, 2H)	380
379	3-Me, 4-Cl	NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (m, 2H), 2.40 (s, 3H), 3.10 (br s, 2H), 3.75 (m, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.55 (d, 1H), 7.85 (m, 1H), 7.95 (s, 1H)	360
380	4-CF_3O	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 4.05 (br d, 2H), 7.20 (t, 2H), 7.50 (m, 4H), 8.10 (d, 2H)	396
381	3-Cl, 4-F	NMR (DMSO-d_6): 1.55 (m, 2H), 1.85 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.25 (m, 2H), 7.45 (m, 2H), 7.50 (m, 1H), 8.00 (m, 1H), 8.10 (m, 1H)	364
382	3,5-di Cl	NMR (DMSO-d_6): 1.55 (m, 2H), 1.85 (m, 2H), 3.15 (t, 2H), 3.75 (m, 1H), 4.00 (m, 2H), 7.25 (t, 2H), 7.45 (m, 2H), 7.80 (s, 1H), 7.90 (s, 2H)	380
383	4-*i*-PrO	NMR (DMSO-d_6): 1.25 (d, 6H), 1.50 (m, 2H), 1.80 (br s, 2H), 3.65 (m, 1H), 4.75 (m, 1H), 7.00 (d, 2H), 7.25 (t, 2H), 7.45 (m, 2H), 7.95 (d, 2H)	370

Ex	$(R^1)_n$	NMR	M/z
384	3-MeO, 4-Cl	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.20 (t, 2H), 3.70 (m, 1H), 3.95 (s, 3H), 4.00 (m, 2H), 7.25 (t, 2H), 7.45 (m, 2H), 7.55 (m, 3H)	376
385	3,4-di Cl	NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (br s, 2H), 3.10 (br s, 2H), 3.75 (m, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.80 (d, 1H), 7.95 (d, 1H), 8.20 (s, 1H)	380
386	3-Me, 4-MeO	NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (m, 2H), 2.20 (s, 3H), 3.75 (m, 1H), 3.85 (s, 3H), 7.00 (d, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.80 (s, 1H), 7.90 (m, 1H)	356
387	3-MeS	NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (br s, 2H), 2.50 (s, 3H), 3.10 (br s, 2H), 3.75 (m, 1H), 7.25 (t, 2H), 7.45 (br m, 4H), 7.75 (m, 2H)	358
388	2,4-di F		348
389 [1]	4-Cl, 3-($PhCH_2OCH_2$-)	NMR (DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 3.10 (m, 2H), 3.65 (m, 1H), 4.00 (br d, 2H), 4.65 (s, 2H), 4.70 (s, 2H), 7.20 (t, 2H), 7.35 (br m, 4H), 7.45 (m, 2H), 7.60 (d, 1H), 7.90 (d, 1H), 8.10 (s, 1H)	466
390 [2]	4-*i*-PrS	NMR (DMSO-d_6): 1.30 (d, 6H), 1.60 (m, 2H), 1.85 (m, 2H), 3.15 (m, 2H), 3.70 (m, 2H), 4.00 (br d, 2H), 7.20 (t, 2H), 7.45 (m, 4H), 7.90 (d, 2H)	386
391	3-EtO	NMR (DMSO-d_6): 1.30 (t, 3H), 1.50 (m, 2H), 1.80 (br s, 2H), 3.75 (m, 1H), 4.10 (q, 2H), 7.25 (m, 3H), 7.45 (m, 4H), 7.55 (d, 1H)	356
392 [3]	4-Cl-3-($MeOCH_2$-)	NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 3.20 (m, 2H), 3.40 (s, 3H), 3.70 (m, 1H), 4.00 (m, 2H), 4.60 (s, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.55 (d, 1H), 7.90 (d, 1H), 8.00 (s, 1H)	390

[1] Starting material: Method 10

[2] Starting material: J. Med. Chem., (1998), 41(26), 5198-5218

[3] Starting material: Method 11

Example 393

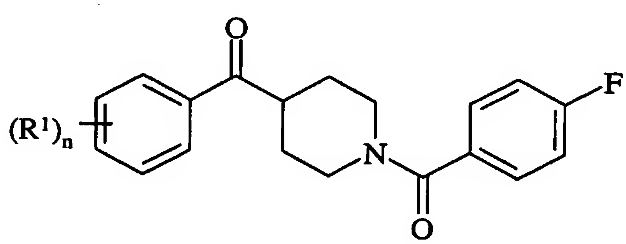
1-(4-Fluorobenzoyl)-4-(3-trifluoromethoxybenzoyl)piperidine

A suspension of Rieke magnesium (100mg) in THF (4ml) was placed in a tube. To this suspension was added a solution of 1-bromo-3-(trifluoromethoxy)benzene (1g,

4.1mmols) in THF (2ml). The resultant reaction was stirred at room temperature for 20 minutes before the addition of a solution of 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxy carbamoyl)piperidine (Method 2; 301mg, 1mmol) in THF (3ml). The reaction was then left to stir for 2.5 hours before quenching with saturated NH_4Cl solution. The reaction was then treated with water (2ml), capped and shaken the allowed to settle. The organic layer was decanted off and evaporated to yield an oil. This oil was purified by column chromatography (40g Si, 20 to 100% EA/isohexane) to yield the product as a white solid (86mg, 21%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (br m, 1H), 3.75 (m, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.70 (m, 2H), 7.90 (s, 1H), 8.05 (d, 1H); m/z 396.

Examples 394-395

The procedure described in Example 393 was repeated using the appropriate reagent to replace the "1-bromo-3-(trifluoromethoxy)benzene" to obtain the compounds described below.



Ex	$(R^1)_n$	NMR	M/z
394	3-*i*-PrO	NMR (DMSO-d_6): 1.25 (d, 6H), 1.50 (m, 2H), 1.80 (m, 2H), 3.75 (m, 1H), 4.70 (m, 1H), 7.20 (m, 1H), 7.25 (m, 2H), 7.40 (m, 4H), 7.55 (d, 1H)	370
395 [1]	3-BuO	NMR (DMSO-d_6): 0.90 (t, 3H), 1.45 (m, 4H), 1.70 (m, 2H), 1.80 (br s, 2H), 3.70 (m, 1H), 4.00 (m, 2H), 7.20 (m, 1H), 7.25 (t, 2H), 7.45 (m, 4H), 7.60 (m, 1H)	384

[1] Starting Material: J. Med. Chem., 40, 23, 1997, 3804-3819

Examples 396

1-(4-Fluorobenzoyl)-4-(4-methylsulphonylbenzoyl)piperidine; and

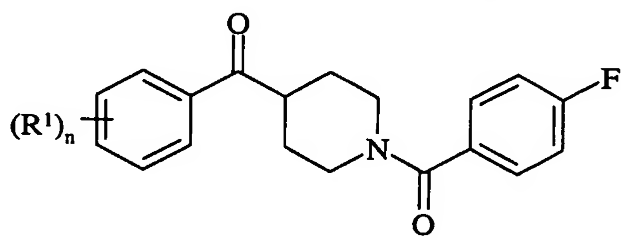
Example 397

1-(4-Fluorobenzoyl)-4-(4-methylsulphinylbenzoyl)piperidine; and

To a stirred solution of 1-(4-fluorobenzoyl)-4-(4-methylthiobenzoyl)piperidine (Example 376; 250mg, 0.7mmols) in THF (5ml) was added 3-chloroperoxybenzoic acid (75%) (242mg, 1.05mmols). The resulting reaction was stirred at room temperature for two hours then transferred to a separating funnel. The reaction mixture was washed with 1M NaOH (3ml), the layers were separated and the aqueous re-extracted with EtOAc (5ml). The combined organics were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield a solid. This solid was purified by column chromatography (5g Si, EtOAc to 10% MeOH/EtOAc) to yield both compounds. Example 396: NMR (DMSO-d_6): 1.65 (m, 2H), 1.90 (m, 2H), 3.20 (t, 2H), 3.25 (s, 3H), 3.75 (m, 1H), 4.00 (br d, 2H), 7.25 (t, 2H), 7.45 (m, 2H), 8.05 (d, 2H), 8.15 (d, 2H); m/z 390. Example 397: NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.80 (s, 3H), 3.20 (m, 2H), 3.75 (m, 1H), 4.00 (br d, 2H), 7.25 (t, 2H), 7.45 (m, 2H), 7.80 (d, 2H), 8.10 (d, 2H); m/z 374.

Examples 398-400

The procedure described in Examples 396 and 397 was repeated using the appropriate reagent to replace Example 376 to obtain the compounds described below.



Ex	$(R^1)_n$	NMR	M/z	SM
398	3-$MeSO_2$	(DMSO-d_6): 1.50 (m, 2H), 1.80 (br s, 2H), 3.80 (m, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.85 (t, 1H), 8.20 (br d, 1H), 8.35 (br d, 1H), 8.40 (s, 1H)	390	Ex 387
399	3-MeSO	(DMSO-d_6): 1.50 (m, 2H), 1.80 (br s, 2H), 2.80 (s, 3H), 3.80 (m, 1H), 7.25 (t, 2H), 7.45 (m, 2H), 7.75 (t, 1H), 7.95 (d, 1H), 8.15 (d, 1H), 8.25 (s, 1H)	374	Ex 387
400	4-iPr-$S(O)_2$-	(DMSO-d_6): 1.20 (d, 6H), 1.60 (m, 2H), 1.90 (m, 2H), 3.15 (m, 2H), 3.45 (m, 1H), 3.75 (m, 1H), 4.05 (m, 2H), 7.25 (t, 2H), 7.50 (m, 2H), 8.00 (d, 2H), 8.20 (d, 2H)	418	Ex 390

Ex	$(R^1)_n$	NMR	M/z	SM
401	4-iPr-S(O)-	(DMSO-d_6): 1.00 (d, 3H), 1.20 (d, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 3.05 (m, 2H), 3.15 (m, 2H), 3.75 (m, 1H), 4.00 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H), 7.75 (d, 2H), 8.10 (d, 2H)	402	Ex 390

Example 402

1-(4-Methylbenzoyl)-4-(4-dimethylaminobenzoyl)piperidine

A vial charged with 1-(4-methylbenzoyl)-4-(4-fluorobenzoyl)piperidine (Example 187; 80mg, 0.25mmols), morpholine (45mg, 0.52mmols) and DMF (4ml) was heated at 190°C for 45 minutes in a microwave. The process was repeated three times and the resulting crude reaction mixtures were combined for work up and purification. The volatiles were removed under reduced pressure and the resulting oil was purified by column chromatography (20g Silica, 20 to 60% EtOAc/isohexane) to yield the product as a solid (118mg, 29%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.70 (br s, 2H), 2.30 (s, 3H), 3.00 (s, 6H), 3.60 (m, 1H), 6.70 (d, 2H), 7.25 (m, 4H), 7.85 (d, 2H); m/z 351.

Example 403

1-(4-Methylbenzoyl)-4-(4-cyanobenzoyl)piperidine

A vial charged with 1-(4-methylbenzoyl)-4-(4-fluorobenzoyl)piperidine (Example 187; 80mg, 0.24mmols), KCN (16mg, 0.24mmols) and DMF (4ml) was heated in a microwave at 180°C for 55 minutes. This procedure was repeated twice then the three crude reaction mixtures were combined and evaporated under reduced pressure. The resulting orange solid was partitioned between EtOAc (30ml) and water (30ml), the organic layer was separated and then washed with brine (15ml), dried ($MgSO_4$), filtered and evaporated to yield a gummy solid. Recrystallisation with EtOH yielded 40mg of the title compound. The EtOH filtrate was then evaporated and the residue was purified by column chromatography (10g Silica, 20 to 60% EtOAc/isohexane) to yield a further 46 mg of material. NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.40 (s, 3H), 3.20 (t, 2H), 3.75 (m, 1H), 4.05 (br d, 2H), 7.30 (m, 4H), 7.90 (d, 2H), 8.10 (d, 2H); m/z 333.

Example 404

1,4-Bis-(4-fluorobenzoyl)-4-methylpiperidine

To a stirred solution of 1,4-bis-(4-fluorobenzoyl)piperidine (Example 8; 200mg, 0.61mmol) in anhyd THF (5ml) was added a 1M solution of lithium bis(trimethyl)amide in THF (1.53ml, 1.53mmol). The reaction was stirred at room temperature for 15 minutes before the addition of MeI (346mg, 2.44mmols). The reaction was then left to stir overnight at room temperature. Water (2ml) was added to the reaction then the volatiles were removed under reduced pressure. The product was partitioned between 1M HCl (15ml) and DCM (20ml). The organic layer was then separated and washed with sat $NaHCO_3$ (15ml) and brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a solid (83mg, 39%). NMR (DMSO-d_6): 1.40 (s, 3H), 1.65 (m, 2H), 2.10 (m, 2H), 3.35 (m, 2H), 3.60 (m, 2H), 7.25 (m, 4H), 7.45 (m, 2H), 7.80 (m, 2H); m/z 344.

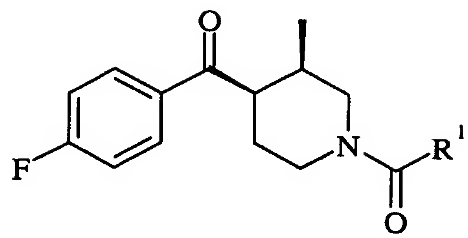
Example 405

3,4-Cis-1,4-Bis-(4-fluorobenzoyl)-3-methylpiperidine

To a stirred solution of 3-methyl-4-(4-fluorobenzoyl)piperidine hydrochloride (Method 4; 119mg, 0.46mmol) and triethylamine (140mg, 1.39mmol) in DCM (4ml) was added 4-fluorobenzoyl chloride (66mg, 0.41mmol). The reaction was stirred at room temperature for 30 minutes then worked up. Reaction transferred to a separating funnel, diluted to 10ml with DCM then washed with 1M HCl (2 x 5ml), sat $NaHCO_3$ (5ml) and brine (5ml). The organic layer was then dried ($MgSO_4$), filtered and evaporated to yield a solid (101mg, 71%). NMR (DMSO-d_6): 0.70 (d, 3H), 1.60 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 3.20 (m, 1H), 3.40 (m, 1H), 3.80 (m, 2H), 3.95 (br m, 1H), 7.25 (t, 2H), 7.30 (t, 2H), 7.45 (m, 2H), 8.05 (m, 2H); m/z 344.

Examples 406-407

The procedure described in Example 405 was repeated using the appropriate reagent to replace the "4-fluorobenzoyl chloride" to obtain the compounds described below (wherein the stereochemistry depicted in the below formula is relative rather than absolute, i.e. the compounds are the cis isomers).



Ex	R^1	NMR	M/z
406	Cyclopropyl	NMR (DMSO-d_6): 0.70 (m, 7H), 1.60 (m, 1H), 1.90 (m, 2H), 2.20 (m, 1H), 3.10 (br m, 1H), 3.40 (br d, 1H), 3.80 (m, 1H), 4.05 (m, 1H), 4.25 (m, 1H), 7.30 (t, 2H), 8.00 (m, 2H)	290
407	Thien-2-yl	NMR (DMSO-d_6): 0.70 (d, 3H), 1.65 (m, 1H), 1.95 (m, 1H), 2.30 (m, 1H), 3.30 (m, 1H), 3.50 (m, 1H), 3.90 (m, 1H), 4.10 (m, 1H), 4.20 (m, 1H), 7.10 (m, 1H), 7.30 (t, 2H), 7.35 (m, 1H), 7.70 (m, 1H), 8.10 (m, 2H)	332

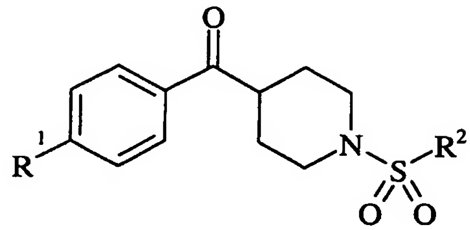
Example 408

1-(Thien-2-ylsulphonyl)-4-(4-chlorobenzoyl)piperidine

To a stirred solution of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (100mg, 0.41mmol) and triethylamine (104mg, 1.03 mmol) in DCM (4ml) was added 2-thiophenesulphonyl chloride (71mg, 039mmol). The reaction was stirred at room temperature for 1 hour then diluted to approximately 10ml with DCM and transferred to a sep funnel. The solution was then washed with 2M HCl (5ml), water (5ml) and brine (5ml), then dried, filtered and evaporated to yield the product as a solid (83mg, 55%). NMR (DMSO-d_6): 1.55 (m, 2H), 1.90 (d, 2H), 2.55 (m, 2H), 3.50 (m, 1H), 3.65 (d, 2H), 7.30 (s, 1H), 7.50 (d, 2H), 7.60 (br s, 1H), 8.00 (d, 2H), 8.05 (m, 1H); m/z 370.

Examples 409-426

The procedure described in Example 408 was repeated using the appropriate reagent to replace the "2-thiophenesulphonyl chloride" to obtain the compounds described below. In some cases a base wash was also carried out ($NaHCO_3$) prior to washing with brine.



Ex	R[1]	R[2]	NMR	M/z
409	F	2-CF_3 phenyl		416
410	F	2-Br phenyl		426
411	F	3-Br phenyl	(DMSO-d_6): 1.55 (m, 2H), 1.85 (br d, 2H), 3.45 (t, 1H), 3.70 (br d, 2H), 7.30 (t, 2H), 7.60 (t, 1H), 7.80 (d, 1H), 7.90 (s, 1H), 7.95 (d, 1H), 8.00 (m, 2H)	426
412	F	3-CF_3 phenyl		416
413	F	4-Cl phenyl		382
414	F	2-Cl, 4-CN phenyl		407
415 [2]	F	3-Cl, 4-NH_2 phenyl	(DMSO-d_6): 1.55 (m, 2H), 1.85 (d, 2H), 2.40 (m, 2H), 3.45 (m, 1H), 3.60 (d, 2H), 6.30 (s, 2H), 6.90 (d, 1H), 7.30 (t, 2H), 7.40 (d, 1H), 7.50 (s, 1H), 8.00 (m, 2H)	397
416	F	4-MeO phenyl		378
417 [1]	F	4-F benzyl	1.45 (m, 2H), 1.80 (d, 2H), 2.90 (t, 2H), 3.55 (m, 3H), 4.40 (s, 2H), 7.20 (t, 2H), 7.35 (t, 2H), 7.45 (m, 2H), 8.05 (m, 2H)	
418	Me	4-F phenyl		362
419	F	4-F phenyl		366
420	MeO	4-F phenyl		378
421	Cl	4-F phenyl	1.90 (m, 4H), 2.60 (m, 2H), 3.20 (m, 1H), 3.75 (m, 2H), 7.25 (m, 2H), 7.40 (d, 2H), 7.80 (m, 4H)	
422	Cl	Iso propyl	1.35 (d, 6H), 1.90 (m, 4H), 3.25 (m, 3H), 3.40 (m, 1H), 3.85 (m, 2H), 7.45 (d, 2H), 7.85 (d, 2H)	330
423	Cl	Benzyl	1.80 (br m, 4H), 2.85 (m, 2H), 3.25 (m, 1H), 3.60 (m, 2H), 4.25 (s, 2H), 7.40 (br m, 7H), 7.85 (d, 2H)	

Ex	R[1]	R[2]	NMR	M/z
424	Cl	4-Me phenyl	1.90 (m, 4H), 2.45 (s, 3H), 2.55 (m, 2H), 3.10 (m, 1H), 3.80 (m, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.65 (d, 2H), 7.80 (d, 2H)	378
425	Cl	Me	2.00 (m, 4H), 2.85 (s, 3H), 3.00 (m, 2H), 3.35 (m, 1H), 3.80 (m, 2H), 7.45 (d, 2H), 7.85 (d, 2H)	302
426	MeO	4-Me phenyl	1.90 (m, 4H), 2.45 (s, 3H), 2.55 (m, 2H), 3.15 (m, 1H), 3.75 (m, 2H), 3.85 (s, 3H), 6.90 (d, 2H), 7.35 (d, 2H), 7.65 (d, 2H), 7.85 (d, 2H)	374

[1] Product purified by column chromatography (10g Silica, 40% EtOAc/isohexane) to yield white solid.

[2] The sulphonylchloride used was 4-acetamido-3-chlorobenzenesulfonyl chloride, the acetyl group was removed during the reaction/work up.

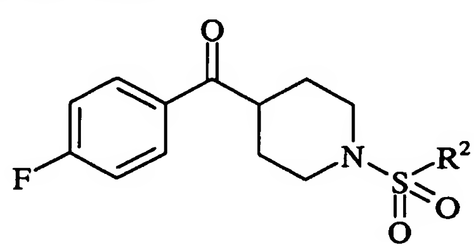
Example 427

1-(3-Chlorophenylsulphonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorbenzoyl)piperidine hydrochloride (51mg, 0.21mmol) and triethylamine (52mg, 0.51 mmol) in DCM (8ml) was added 3-chlorobenzenesulfonyl chloride (40mgs, 0.19m.mol) The reaction was stirred at room temperature for 16 hours. The solution was then washed with 2M HCl (5ml), saturated sodium carbonate (5ml) and water (5ml) using a Mettler Toledeo Myriad ALLEX liquid –liquid extractor then dried, filtered and evaporated to yield the product as a solid (58.8mgs, 62.4%). M/z 382.

Examples 428-456

The procedure described in Example 427 was repeated using the appropriate reagents to obtain the compounds described below.



Ex	R^2	M/z
428	2,5-Dimethylphenyl	375
429	2-Chloro-6-methylphenyl	396
430	5-Fluoro-2-methylphenyl	379
431	2-Methylphenyl	361
432	2-Chlorophenyl	382
433	2,5-Dichlorothien-3-yl	422
434	2-Fluorophenyl	365
435	2,4,5-Trifluorophenyl	401
436	3-Fluorophenyl	365
437	3,5-Dimethylisoxazol-4-yl	366
438	2-Cyanophenyl	372
439	2-Nitro-4-methoxyphenyl	422
440	4-Ethylphenyl	375
441	2-Chloro-4-flurophenyl	400
442	2-Methoxy-5-methylphenyl	391

Ex	R^2	M/z
443	3-Methoxyphenyl	377
444	2,4-Difluorophenyl	383
445	Thien-3-yl	353
446	3-Methylphenyl	361
447	5-Chloro-1,3-dimethylpyrazol-4-yl	400
448	Butyl	327
449	4-Bromophenyl	426
450	Isopropyl	313
451	4-Methylphenyl	361
452	4-Trifluoromethylphenyl	415
453	4-Acetamidophenyl	404
454	2-Chlorothien-5-yl	388
455	2,6-Diflurophenyl	383
456	Ethyl	299

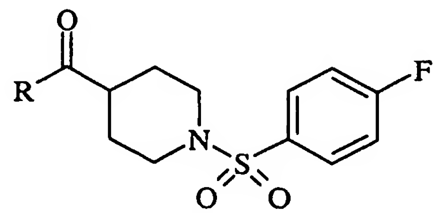
Example 457

1-(4-Fluorophenylsulphonyl)-4-(3-methoxybenzoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 8; 250mg, 0.76mmol) in anhydrous THF (5ml) at 0°C was added a 1M solution of 3-methoxyphenylmagnesium bromide in THF (2.66ml, 2.66mmol). The reaction was stirred at 0°C for ten minutes then allowed to warm temperature and stirred for a further 30 minutes. The reaction was quenched with sat NH_4Cl solution then extracted with EtOAc (2x15ml). The organic layers were combined, washed with brine (10ml), dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 20% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a white solid (115mg, 40%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.70 (m, 2H), 3.50 (m, 1H), 3.70 (m, 2H), 3.85 (s, 3H), 7.20 (m, 1H), 7.50 (m, 5H), 7.85 (m, 2H); m/z 378.

Examples 458-464

The procedure described in Example 457 was repeated using the appropriate reagent to replace the "3-methoxyphenylmagnesium bromide" to obtain the compounds described below.



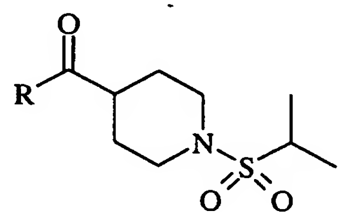
Ex	R	NMR	M/z
458	3-Me phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.40 (s, 3H), 2.70 (t, 2H), 3.45 (m, 1H), 3.70 (m, 2H), 7.45 (m, 4H), 7.70 (m, 2H), 7.90 (m, 2H)	362
459 [1]	2-Me phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.85 (m, 2H), 2.30 (s, 3H), 2.65 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 7.25 (m, 2H), 7.35 (m, 1H), 7.40 (m, 2H), 7.55 (d, 1H), 7.80 (m, 2H)	362
460	2- MeO phenyl	(DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 2.65 (m, 2H), 3.20 (m, 1H), 3.65 (m, 2H), 3.80 (s, 3H), 7.00 (t, 1H), 7.15 (d, 1H), 7.45 (m, 4H), 7.80 (m, 2H)	378
461	3,5-di F phenyl	1.50 (m, 2H), 1.85 (br d, 2H), 2.45 (m, 2H), 3.45 (m, 1H), 3.65 (d, 2H), 7.50 (m, 3H), 7.65 (m, 2H), 7.85 (m, 2H)	384
462 [3]	2,4-di F Benzyl	1.50 (m, 2H), 1.95 (m, 2H), 2.35 (m, 2H), 2.55 (m, 1H), 3.60 (d, 2H), 3.85 (s, 2H), 7.00 (m, 1H), 7.15 (m, 1H), 7.25 (m, 1H), 7.50 (t, 3H), 7.85 m, 2H)	398
463 [2]	2-Me, 4-F phenyl	1.55 (m, 2H), 1.85 (m, 2H), 2.30 (s, 3H), 2.60 (m, 2H), 3.20 (m, 1H), 3.65 (m, 2H), 7.10 (m, 2H), 7.40 (t, 2H), 7.70 (m, 1H), 7.85 (m, 2H)	380
464 [2]	2,4-di Me phenyl	1.55 (m, 2H), 1.85 (m, 2H), 2.30 (d, 6H), 2.65 (m, 2H), 3.20 (m, 1H), 3.60 (m, 2H), 7.05 (m, 2H), 7.40 (t, 2H), 7.50 (d, 1H), 7.85 (m, 2H)	376

[1] The material recovered from the initial chromatography was purified by prep LCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN).

[2] The material recovered from the initial chromatography was purified by prep LCMS (5-95% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN).
[3] The product was purified by an EtOAc recrystallization.

Examples 465-466

The procedure described in Example 457was repeated using the appropriate reagent to replace the "3-methoxyphenylmagnesium bromide" and 1-(isopropylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 9) to obtain the compounds described below.



Ex	R	NMR	M/z
465	3,5-di F phenyl	(DMSO-d_6): 1.20 (d, 6H), 1.50 (m, 2H), 1.85 (br d, 2H), 3.05 (t, 2H), 3.30 (m, 1H), 3.65 (m, 3H), 7.55 (m, 1H), 7.65 (m, 2H)	332
466	2,4 di F benzyl	1.20 (d, 6H), 1.45 (m, 2H), 1.90 (br d, 2H), 2.70 (m, 1H), 2.95 (t, 2H), 3.30 (m, 2H), 3.65 (br d, 2H), 3.90 (s, 2H), 7.00 (m, 1H), 7.15 (m, 1H), 7.25 (m, 1H)	346

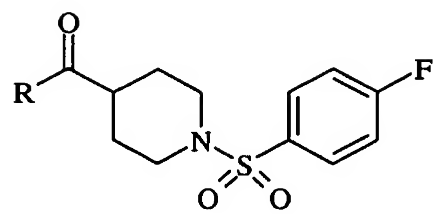
Example 467

1-(4-Fluorophenylsulphonyl)-4-(3-fluorobenzoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxy carbamoyl)piperidine (Method 8; 36mg, 0.11mmol) in anhydrous THF (1ml) was added a 0.5M solution of 3-flurophenyl magnesium bromide in THF (0.78ml, 0.39mmol). The reaction was stirred at room temperature for 3 hours then quenched with sat NH_4Cl solution. Water (1ml) and EtOAc (3ml) were added and the reaction was capped and briefly shaken then allowed to settle. The organic layer was transferred to a weighed vial then evaporated to yield crude product. This was purified by prep LCMS to yield a gum (9mg, 20%). M/z 366.

Examples 468-474

The procedure described in Example 467 was repeated using the appropriate reagent to replace the "3-flurophenyl magnesium bromide" to obtain the compounds described below.



Ex	R	M/z
468	4-*t*-Butylphenyl	404
469	1,3-Benzodioxol-5-yl	392
470	6-Methylpyrid-2-yl	363
471 [1]	4-propyphenyl	390

Ex	R	M/z
472	5-Chlorothie-2-yl	388
473	Pyrid-2-yl	349
474	Thien-2-yl	354

[1] NMR: (DMSO-d_6): 0.85 (t, 3H), 1.55 (m, 4H), 1.80 (br d, 2H), 2.60 (t, 2H), 3.40 (m, 1H), 3.65 (m, 2H), 7.30 (d, 2H), 7.50 (t, 2H), 7.85 (m, 4H)

Example 475

1-(4-Fluorophenylsulphonyl)-4-(4-fluorobenzoyl)-4-ethylpiperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(4-fluorobenzoyl)piperidine (Example 419; 200mg, 0.55mmol) in anhydrous THF (5ml) at 0°C was added a 1M solution of lithium bis(trimethyl)amide in THF (1.1ml, 1.1mmol). The reaction was allowed to stir briefly before the addition of ethyl iodide (171mg, 1.1mmol). The reaction was then allowed to warm to room temperature and left to stir overnight. The volatiles were removed under reduced pressure and the resulting gummy solid was partitioned between water and EtOAc. The organic layer was separated then washed with brine, dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (20g Silica, 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a white solid (16mg, 7%). NMR (DMSO-d_6): 0.70 (t, 3H), 1.65 (m, 2H), 1.85 (q, 2H), 2.25 (br d, 2H), 2.40 (m, 2H), 3.35 (m, 2H), 7.25 (t, 2H), 7.50 (t, 2H), 7.70 (m, 2H), 7.80 (m, 2H); m/z 394.

Example 476

1-(Thien-2-ylmethyl)-4-(4-chlorobenzoyl)piperidine

To a stirred suspension of (4-chlorophenyl)(4-piperidyl)methanone hydrochloride (200mg, 0.82mmol) in THF (6ml) was added 2-thiophene carboxaldehyde (101mg, 0.90mmol). The reaction was stirred at 35°C for 5 hours before the addition of sodium triacetoxyborohydride (434mg, 2.05mmol). The reaction was left to stir at 35°C for 48 hours before quenching by the addition of water (10ml). Volatiles removed under reduced pressure

and the resulting solid was partitioned between water and DCM. The DCM layer was separated off and the aqueous was reextracted with DCM. The organic phases were combined and washed with brine, then dried, filtered and evaporated to yield crude product. This crude product was dissolved in DCM and treated with PS-trisamine (60mg) and PS-tosylchloride (290mg) for 12 hours. The polymer bound reagents were filtered off and the solvent was removed to yield the product (98mg, 38%). NMR: 1.85 (m, 4H), 2.00 (m, 2H), 3.00 (m, 2H), 3.20 (m, 1H), 3.75 (s, 2H), 6.95 (m, 2H), 7.25 (m, 1H), 7.40 (d, 2H), 7.85 (d, 2H).

Example 477

1-(Benzyl)-4-(4-bromobenzoyl)piperidine

To a stirred solution of ethyl-N-benzyl isonipecotate (5.7g, 24.2mmol) in methanol (60ml) was added a 1M solution of NaOH (60ml, 60mmol). The resulting mixture was stirred for 4 hours. The solution was neutralised by the addition of 2M HCl solution (30ml, 60mmol) then the solvent was removed *in vacuo*. The residue was triturated with THF (3x100ml), the triturates were combined and evaporated to give 4.12g of N-benzylisonipecotic acid which was used without further purification. The N-benzylisonipecotic acid (3.94g, 18.0mmol) was suspended in THF (100ml) under Argon then cooled to –78°C. A 2M solution of lithium diisopropylamide was then added dropwise with stirring (22.5ml, 45mmol). The reaction was then allowed to warm to room temperature followed by refluxing under argon for a further hour (oil bath temperature 50°C). This solution was then allowed to cool back to room temperature. In a separate flask 4-bromobenzoyl chloride (5.93g, 27mmol) was dissolved in THF (100ml) and cooled to –78°C. The dianion solution was added dropwise to the acid chloride solution over 30 minutes. The reaction mixture was stirred at –78°C for a further 30 minutes then allowed to warm to room temperature over night. The reaction was quenched by the addition of 2M HCl (36ml, 72mmol) in 100g of crushed ice. The product was extracted with 3x200ml DCM, dried over $MgSO_4$ and then evaporated to give a brown oil. Flash column chromatography was performed, eluting with 0 to 5% MeOH in DCM. 1.7g of pure material was obtained as an orange solid. M/z 358.

Example 478

1-(Pyrimidin-2-yl)-4-(4-fluorobenzoyl)piperidine

A solution of 4-(4-flurobenzoyl)piperidine hydrochloride (300mg, 1.23mmol), 2-chloropyrimidine (141mg, 1.23mmol) and triethylamine (261mg, 2.58mmol) in EtOH (10ml)

was stirred at reflux for 5 hours. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. The crude product was partitioned between EtOAc (20ml) and water (20ml). The organic layer was separated, washed with brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield crude product. This material was purified by column chromatography (DCM eluent) to yield the product as an oil which crystallised on standing (123mg, 35%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.83 (br d, 2H), 3.10 (m, 2H), 3.75 (m, 1H), 4.65 (br d, 2H), 6.60 (t, 1H), 7.35 (t, 2H), 8.10 (m, 2H), 8.30 (d, 2H); m/z 286.

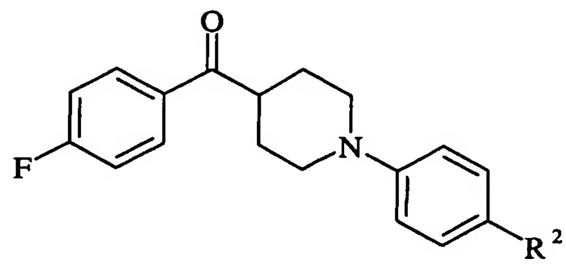
Example 479

1-(4-Trifluoromethylphenyl)-4-(4-fluorobenzoyl)piperidine

Copper iodide (10mg, 0.05mmol), K_3PO_4 (636mg, 3mmol) and 4-(4-fluorobenzoyl)piperidine hydrochloride (292mg, 1.2mmol) were put into a glass tube. The tube was sealed with a subaseal and evacuated and back filled with Argon. This Argon purge was repeated three times. Isopropanol (1ml), ethylene glycol (111μl) and 4-iodobenzotrifluoride (272mg, 1mmol) were then added by syringe. The reaction was warmed to 75°C and left to stir at this temperature over night. The reaction was cooled to room temperature and partitioned between water (10ml) and ether (15ml). The layers were separated and the aqueous layer was reextracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, eluting with 10% EtOAc/isohexane to 40% EtOAc/isohexane) to yield a solid (54mg, 15%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.85 (br d, 2H), 3.00 (t, 2H), 3.70 (m, 1H), 3.90 (br d, 2H), 7.05 (d, 2H), 7.35 (t, 2H), 7.45 (d, 2H), 8.10 (m, 2H); m/z 352.

Examples 480-483

The procedure described in Example 479 was repeated using the appropriate reagent to replace the "4-iodobenzotrifluoride" to obtain the compounds described below. In cases where the "iodo" compound was a solid it was added at the start of the reaction prior to the Argon purge.



Ex	R^2	NMR	M/z
480	MeO	(DMSO-d_6): 1.75 (m, 2H), 1.90 (br d, 2H), 2.85 (m, 2H), 3.55 (m, 3H), 3.70 (s, 3H), 6.80 (d, 2H), 6.90 (d, 2H), 7.30 (t, 2H), 8.05 (m, 2H)	314
481	MeC(O)NH-	(DMSO-d_6): 1.65 (m, 2H), 1.85 (br d, 2H), 2.00 (s, 3H), 2.80 (m, 2H), 3.55 (m, 1H), 1.60 (br d, 2H), 6.85 (d, 2H), 7.40 (m, 4H), 8.10 (m, 2H), 9.65 (s, 1)	341
482	F	(DMSO-d_6): 1.65 (m, 2H), 1.85 (br d, 2H), 2.80 (m, 2H), 3.55 (m, 1H), 3.60 (br d, 2H), 6.95 (m, 2H), 7.00 (t, 2H), 7.35 (t, 2H), 8.10 (m, 2H)	302
483	MeC(O)-	(DMSO-d_6): 1.60 (m, 2H), 1.85 (br d, 2H), 2.40 (s, 3H), 3.10 (m, 2H), 3.70 (m, 1H), 4.00 (br d, 2H), 7.00 (d, 2H), 7.35 (t, 2H), 7.80 (d, 2H), 8.10 (m, 2H)	326

Example 484

1-(Pyrid-4-yl)-4-(4-methoxybenzoyl)piperidine

To a stirred suspension of 1-(pyrid-4-yl)-4-(carboxy)piperidine (10.31 g, 50 mmol) in DCM (200 ml) at 4°C, was added oxalyl chloride (13 ml, 151.3 mmol) and DMF (cat). The mixture was allowed to warm to ambient temperature and stirred for 18 hours. Volatile material was removed by evaporation to give a solid. This solid was added slowly to a stirred mixture of aluminium chloride (40.0 g, 300 mmol) and anisole (40 ml, 368 mmol). The mixture was heated to 85°C and stirred for 3 hours, then allowed to cool to ambient temperature and stirred for a further 16 hours. The mixture was poured onto an ice/water mix. This was extracted with DCM (400 ml). The extract was washed with water (150 ml), brine (50 ml), water (2 x 200 ml) and dried over $MgSO_4$. Volatile material was removed by evaporation to leave a solid, which was purified by flash chromatography, eluting with 5-10% methanol in DCM to give a solid. This was recrystallized from ethanol to give the title compound (0.839 g) a solid. NMR (d_6-DMSO): 1.55 (m, 2H), 1.78 (m, 2H), 3.00 (t, 2H), 3.68

(m, 1H), 3.83 (s, 3H), 3.94 (m, 2H), 6.80 (d, 2H), 7.03 (d, 2H), 7.98 (d, 2H), 8.10 (d, 2H), MS: (ESP$^+$) m/z 297.0.

Example 485

1-(6-Chloronaphth-2-ylmethyl)-4-(4-fluorobenzoyl)piperidine

A solution containing 2-chloro-6-chloromethylnaphthalene (European Journal of Medicinal Chemistry (1984), 19(3), 205-14; 0.11g; 0.5mmol) in DMF (3ml) was added to 4-(4-fluorobenzoyl)piperidine hydrochloride (weighed at 0.5mmol) in DMF (3ml). Solid potassium carbonate was added and the mixture stirred at 100°C for 3 hours. After cooling, the mixture was evaporated to approx. 1 ml and water (7ml) was added. The solid products were collected by filtration and washed with water (1ml).Yield 90%. M/z 382.2.

Example 486

1-(4-Fluoroanilinothiocarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (300mg, 1.22mmol) and triethylamine (134mg, 1.32mmol) in DCM (6ml) was added 4-fluorophenyl isothiocyanate (170mg, 1.1mmol). The reaction was left to stir at room temperature for 15 minutes then worked up. The reaction was transferred to a separating funnel and diluted to approximately 5ml with DCM. The DCM was washed with 1M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (300mg, 68%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.85 (br d, 2H), 3.30 (t, 2H), 3.70 (m, 1H), 4.75 (br d, 2H), 7.10 (t, 2H), 7.30 (m, 2H), 7.35 (t, 2H), 8.10 (m, 2H), 9.25 (s, 1H); m/z 361.

Example 487

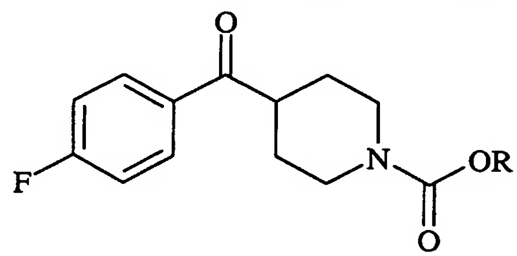
1-(Phenoxycarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred suspension of 4-(4-fluorobenzoyl)piperidine hydrochloride (244mg, 1mmol) in DCM (10ml) was added PS-DIEA, 3.66mmol/g, 683mg. The reaction was stirred for 15 minutes, then phenyl chloroformate (188mg, 1.2mmol) was added. The reaction was stirred for 16hours. PS-Trisamine (3.75mmol/g, 133mg) was added , and stirring was continued for a further hour before filtration through a PTFE phase separating membrane. The product was purified by flash column chromatography (10g Silica), eluting 25% EtOAc in isohexane, and isolated as a white solid (118mg, 36%). NMR (DMSO-d_6): 1.40-1.70 (br s,

2H), 1.86 (d, 2H), 3.00-3.20 (br m, 2H), 3.71 (m, 1H), 4.0-4.3 (br d, 2H), 7.10 (d, 2H), 7.20 (t, 1H), 7.36 (t, 4H), 8.10 (m, 2H). M/z 391.47 $(M+MeCN+Na)^+$.

Examples 488-493 and Reference Examples 7 and 8

Using the procedure given for Example 487, the following Examples were synthesised substituting the phenyl chloroformate with the appropriate chloroformate reagent.



Ex	R	NMR
488	Me	(DMSO-d_6): 1.40 (qd, 2H), 1.76 (d, 2H), 2.97 (t, 2H), 3.58 (s, 3H), 3.59-3.68 (m, 1H), 3.98 (d, 2H), 7.34 (t, 2H), 8.02-8.15 (m, 2H)
RE 7	Et	(DMSO-d_6): 1.17 (t, 3H), 1.40 (qd, 2H), 1.76 (d, 2H), 2.96 (t, 2H), 3.54-3.70 (m, 1H), 3.91-4.10 (m, 4H), 7.34 (t, 2H), 8.00-8.12 (m, 2H)
489	Allyl	(DMSO-d_6): 1.42 (qd, 2H), 1.78 (d, 2H), 2.99 (t, 2H), 3.57-3.71 (m, 1H), 4.01 (d, 2H), 4.51 (d, 2H), 5.21 (dd, 2H), 5.84-6.00 (m, 1H), 7.34 (t, 2H), 8.00-8.13 (m, 2H)
490	$MeOCH_2CH_2$-	(DMSO-d_6): 1.41 (qd, 2H), 1.77 (d, 2H), 2.97 (t, 2H), 3.25 (s, 3H), 3.50 (t, 2H), 3.57-3.71 (m, 1H), 3.99 (d, 2H), 4.10 (t, 2H), 7.34 (t, 2H), 8.00-8.13 (m, 2H)
RE 8	Benzyl	(DMSO-d_6): 1.43 (qd, 2H), 1.78 (d, 2H), 3.01 (t, 2H), 3.56-3.72 (m, 1H), 4.03 (d, 2H), 5.07 (s, 2H), 7.24-7.46 (m, 7H), 8.01-8.15 (m, 2H)
491	Isopropyl	(DMSO-d_6): 1.17 (d, 6H), 1.39 (qd, 2H), 1.75 (d, 2H), 2.94 (t, 2H), 3.55-3.71 (m, 1H), 3.98 (d, 2H), 4.69-4.85 (m, 1H), 7.34 (t, 2H), 8.01-8.12 (m, 2H)
492	4-Fluorophenyl	(DMSO-d_6): 1.41-1.69 (br s, 2H), 1.85 (d, 2H), 2.95-3.25 (b m, 2H), 3.64-3.80 (m, 1H), 3.97-4.29 (br d, 2H), 7,11-7.25 (m, 4H), 7.36 (t, 2H), 8.03-8.17 (m, 2H)

Ex	R	NMR
493	4-Methoxy phenyl	(DMSO-d_6): 1.40-1.70 (br s, 2H), 1.84 (d, 2H), 2.90-3.25 (br s, 2H), 3.61-3.79 (m, 4H), 3.93-4.28 (br s, 2H), 6.89 (d, 2H), 7.03 (d, 2H), 7.36 (t, 2H), 8.01-8.17 (m, 2H)

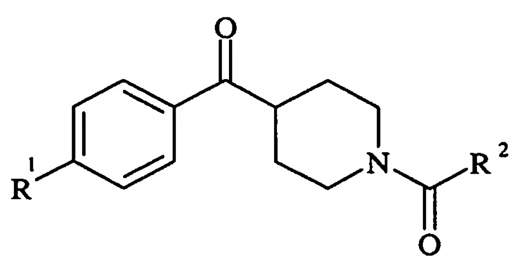
Example 494

1-(4-Fluoroanilinocarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of 4-(4-fluorobenzoyl)piperidine hydrochloride (200mg, 0.82mmol) and triethylamine (87mg, 0.86mmol) in DCM (4ml) was added 4-fluorophenyl isocyanate (101mg, 0.74mmol). The reaction was left to stir at room temperature for 15 minutes then worked up. Reaction transferred to a separating funnel and diluted to approximately 5ml with DCM. The DCM was washed with 1M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (153mg, 54%). NMR (DMSO-d_6): 1.50 (m, 2H), 1.80 (br d, 2H), 2.95 (t, 2H), 3.65 (m, 1H), 4.10 (br d, 2H), 7.05 (t, 2H), 7.35 (t, 2H), 7.45 (m, 2H), 8.10 (m, 2H), 8.50 (s, 1H); m/z 345.

Examples 495-515 and Reference Examples 9 and 10

The procedure described in Example 494 was repeated using the appropriate reagents to replace the "4-(4-fluorobenzoyl)piperidine hydrochloride" and "4-fluorophenyl isocyanate" to obtain the compounds described below.



Ex	R^1	R^2	NMR	M/z
495	6-Bromo naphth-2-yl sulphonyl	Me_2N-	1.25 (m, 2H), 1.73 (d, 2H), 2.70 (s, 6H), 2.80 (t, 2H), 3.53 (m, 3H), 7.82 (d, 1H), 7.97 (d, 1H), 8.15 (m, 6H), 8.36 (s, 1H), 8.78 (s, 1H)	531

Ex	R^1	R^2	NMR	M/z
496	6-Bromo naphth-2-yl sulphonyl	H_2N-	1.33 (m, 2H), 1.70 (d, 2H), 2.80 (t, 2H), 3.57 (m, 1H), 3.90 (d, 2H), 5.87 (s, 2H), 7.82 (d, 1H), 7.97 (d, 1H), 8.15 (m, 6H), 8.36 (s, 1H), 8.78 (s, 1H)	503
497	Cl	Me_2N-	1.40-1.58 (m, 2H), 1.70-1.80 (br d, 2H), 2.73 (s, 6H), 2.78-2.94 (br t, 2H), 3.50-3.63 (br d, 3H), 7.55-7.62 (d, 2H), 7.97-8.03 (d, 2H)	295.43
498	F	$(i\text{-Pr})_2N$-		355.53
499	F	Piperidin-1-yl		319.50
500	Cl	Anilino	1.40-1.62 (m, 2H), 1.73-1.90 (br d, 2H), 2.90-3.08 (app t, 2H), 3.58-3.75 (m, 1H), 4.06-4.24 (br d, 2H), 7.85-7.98 (pp t, 1H), 7.15-7.30 (app t, 2H), 7.38-7.53 (app d, 2H), 7.56-7.68 (app d, 2H), 7.96-8.10 (app d, 2H), 8.40-8.55	343.42
RE 9	F	Me_2N-	1.40-1.68 (m, 2H), 1.68-1.90 (br d, 2H), 2.58-3.0 (m, 8H), 3.50-3.75 (m, 3H), 7.28-7.50 (m, 2H), 8.0-8.22 (m, 2H)	279.46
RE 10	F	3-Chloroanilino		361.42
501	F	Benzylamino		341.8
502	F	Anilino		279.42
503	F	2-Fluoroanilino	1.41-1.62 (m, 2H), 1.74-1.90 (d, 2H), 2.93-3.10 (t, 2H), 3.59-3.75 (m, 1H), 4.03-4.20 (d, 2H), 7.0-7.23 (m, 3H), 7.30-7.50 (m, 3H), 8.0-8.15 (m, 2H), 8.17-8.30 (s, 1H)	345.45
504	F	3,4-Difluoroanilino		363.45
505	F	Morpholino	1.40-1.59 (m, 2H), 1.70-1.82 (br d, 2H), 3.84-2.97 (app br t, 2H), 3.03-3.17 (m, 4H), 3.50-3.70 (m, 7H), 7.27-7.40 (app t, 2H), 8.00-8.13 (m, 2H)	321.47

Ex	R^1	R^2	NMR	M/z
506	F	3-Methylanilino		341.47
507	F	2-Ethylanilino	1.11 (t, 3H), 1.49 (q, 2H), 1.71-1.84 (br d, 2H), 2.54 (q, 2H), 2.99 (t, 2H), 3.60-3.75 (m, 1H), 4.02-4.17 (br d, 2H), 7.02-7.23 (br m, 4H), 7.36 (t, 2H), 7.98 (s, 1H), 8.09 (t, 2H)	
508	F	3-Methyl benzylamino	1.41 (q, 2H), 1.66-1.82 (br d, 2H), 2.27 (s, 3H), 2.88 (t, 2H), 3.55-3.67 (m, 1H), 3.92-4.09 (br d, 2H), 4.19 (d, 2H), 6.92-7.09 (m, 4h), 7.16 (t, 1H), 7.34 (t, 2H), 8.08 (t, 2H)	
509	F	2-Fluoro benzylamino	1.32-1.53 (m, 2H), 1.68-2.25 (br d, 2H), 2.89 (t, 2H), 3.54-3.68 (m, 1H), 3.94-4.07 (br d, 2H), 4.27 (d, 2H), 7.01 (t, 1H), 7.06-7.19 (m, 2H), 7.21-7.44 (m, 3H), 8.02-8.13 (m, 2H)	
510	F	3-Fluoro benzylamino	1.33-1.53 (m, 2H), 1.68-1.82 (br d, 2H), 2.90 (t, 2H), 3.55-3.69 (m, 1H), 3.95-4.09 (br d, 2H), 4.23 (d, 2H), 6.92-7.15 (m, 3H), 7.26-7.40 (m, 3H), 8.02-8.13 (m, 2H)	
511	F	2-Trifluoromethyl anilino	1.40-1.57 (m, 2H), 1.72-1.85 (br d, 2H), 3.00 (t, 2H), 3.61-3.74 (m, 1H), 4.02-4.14 (br d, 2H), 7.30-7.44 (m, 4H), 7.56-7.69 (m, 2H), 8.04-8.13 (m, 2H), 8.17 (s, 1H)	395.47
512	F	2,6-Dimethyl anilino	1.40-1.59 (m, 2H), 1.70-1.85 (br d, 2H), 2.13 (s, 6H), 3.00 (t, 2H), 3.62-3.77 (m, 1H), 4.05-4.12 (br d, 2H), 7.01 (app s, 3H), 7.35 (t, 2H), 7.82 (s, 1H), 8.09 (app t, 2H)	355.53
513	F	2,5-Difluoro anilino	1.39-1.59 (m, 2H), 1.72-1.86 (br d, 2H), 3.01 (t, 2H), 3.59-3.74 (m, 1H), 4.03-4.17 (br d, 2H), 6.80-6.93 (m, 1H), 7.14-7.26 (m, 1H), 7.29-7.45 (m, 3H), 8.02-8.14 (m, 2H), 8.38 (s, 1H)	361.43 $(M-H)^-$

Ex	R^1	R^2	NMR	M/z
514	F	4-Methoxy benzylamino	1.31-1.50 (m, 2H), 1.65-1.78 (br d, 2H), 2.86 (t, 2H), 3.51-3.67 (m, 1H), 3.71 (s, 3H), 3.94-4.06 (br d, 2H), 4.14 (d, 2H), 6.84 (d, 2H), 6.90-7.01 (m, 1H), 7.16 (d, 2H), 7.34 (t, 2H), 8.02-8.12 (m, 2H)	371.51
515	F	(R)-α-Methyl benzylamino	1.29-1.49 (m, 5H), 1.64-1.79 (br d, 2H), 2.84 (t, 2H), 3.51-3.67 (m, 1H), 3.98-4.12 (br d, 2H), 4.75-4.90 (m, 1H), 6.68-6.76 (br d, 1H), 7.11-7.22 (m, 1H), 7.21-7.40 (m, 6H), 8.00-8.12 (m, 2H)	

Example 516

1-[4-(Pyrid-2-yl)anilinocarbonyl]-4-(4-fluorobenzoyl)piperidine

To a stirred suspension of 4-(2-pyridyl)aniline (172mg, 1.01mmol) and PS-DIEA (2 mmol) in DCM (5 ml) was added trichloroacetyl chloride (134 µl, 1.2 mmol). The solutions were stirred for 72 hours. The reaction was filtered and the filtrate evaporated in vacuo. The residue was dissolved in DMSO (3 ml), and treated with sodium carbonate (424 mg, 4 mmol) and 4-fluorobenzoylpiperidine (approx 1mmol dissolved in 2ml DMSO) at 80°C for 6 hours. The reaction mixture was cooled to room temperature, and evaporated under high vacuum. The resultant gum was triturated with EtOAc (10ml) and filtration afforded the product as an off-white solid (135mg, 33%). NMR (DMSO-d_6): 1.41-1.61 (m, 2H), 1.73-1.88 (br d, 2H), 3.01 (t, 2H), 3.59-3.77 (m, 1H), 4.08-4.25 (br d, 2H), 7.18-7.28 (app t, 1H), 7.36 (t, 2H), 7.57 (d, 2H), 7.73-7.90 (m, 2H), 7.96 (d, 2H), 8.03-8.15 (m, 2H), 8.59 (d, 1H), 8.66 (s, 1H); m/z 371.51.

Example 517

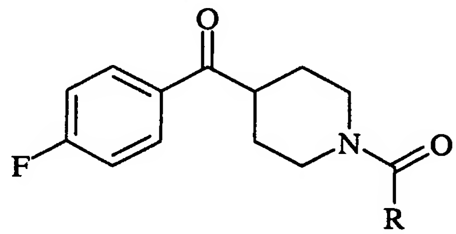
1-(*N*-methyl-4-fluoroanilinocarbonyl)-4-(4-fluorobenzoyl)piperidine

To a stirred solution of triphosgene (297mg, 1.0mmol) in DCM, was added the 4-(4-fluorobenzoyl)piperidine hydrochloride (293mg, 1.2mmol) and DIEA (383µl, 2.2mmol) in one portion. The reaction was left to stir at room temperature for 30 minutes prior to adding the 4-fluoro-N-methylaniline (126mg, 1.0mmol). The reaction mixture was stirred at room temperature overnight then worked up. The reaction was transferred to a separating funnel

and diluted to approximately 5ml with DCM. The DCM was washed with 2M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (65mg, 18%). NMR (DMSO-d_6): 1.2-1.38 (m, 2H), 1.60 (br d, 2H), 2.75 (t, 2H), 3.03 (s, 3H), 3.43-3.58 (m, 1H), 3.70 (br d, 2H), 7.16 (d, 4H), 7.35 (t, 2H), 8.0 (dd, 2H); m/z 359.

Examples 518-521

The following compounds were prepared by the procedure of Example 517.



Ex	R	NMR	M/z
518	4-(4-fluorobenzoyl) piperidin-1-yl	1.41-1.58 (m, 2H), 1.73 (d, 2H), 2.90 (t, 2H), 3.6 (d, 6H), 7.35 (t, 4H), 8.05 (dd, 4H)	441
519	2,6-difluoroanilino	1.41-1.58 (m, 2H), 1.80 (d, 2H), 3.0 (t, 2H), 3.6-3.72 (m, 1H), 4.10 (d, 2H), 7.08 (d, 2H), 7.21-7.30 (m, 1H), 7.31-7.40 (t, 2H), 8.04 (d, 2H)	363; 361 $(M-H)^-$
520	2,3-difluoroanilino		363; 361 $(M-H)^-$
521	*N*-methylanilino	(DMSO-d_6): 1.27 (dt, 2H), 1.58 (br d, 2H), 2.75 (t, 2H), 3.07 (s, 3H), 3.48 (t, 1H), 3.70 (br d, 2H), 7.10 (d, 3H), 7.30 (dd, 4H), 8.01 (dd, 2H)	341

Example 522

1-(4-Fluorobenzoyl)-4-(2-fluorobenzoyl)piperidine

Magnesium (55mg, 2.25mmol) was placed in a flask and covered with ether (6ml). The reaction was briefly stirred under Argon before the addition of a crystal of iodine. The reaction was cooled to 0°C before the slow addition of a solution of 2-fluroiodobezene (500mg, 2.25mmol) in ether (2ml). The reaction was then slowly warmed to 30°C but did not seem to exotherm. At this point 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 1g, 3.38mmol) was added and the reaction was left to stir for 3 hours. The reaction was then quenched with sat NH_4Cl (10ml) and extracted with EtOAc (2 x 10ml).

The combined organic fractions were washed with brine (10ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. Oil purified by column chromatography (10% EtOAc/isohexane to 50% EtOAc/isohexane) to yield an oil. This oil was not clean so the material was further purified by prepLCMS (1-40% over 9.5mins, MeCN/water, with a constant 5ml/min 4% formic acid / MeCN) to yield a solid (1mg, 0.14%). m/z 330.

<u>Example 523</u>

<u>1-(4-Fluorobenzoyl)-4-(pyrid-2-ylcarbonyl)piperidine</u>

Ethyl magnesium bromide (1M soln. in THF - 380µl, 0.38mmol) was added to a solution of 2-iodopyridine (70mg, 0.34mmol) in THF (4mls) at room temperature under an inert atmosphere. After stirring for 40 minutes, 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 120mg, 0.41mmol) was added as a solution in THF (1ml). After stirring at room temperature overnight, more Grignard reagent (1.36mmol – generated as before) was added. The reaction mixture was stirred for a further 64h before being quenched with saturated ammonium chloride solution (10ml). The mixture was extracted with DCM (2x10ml) before drying ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was purified by column chromatography (50% EtOAc/isohexane – 80% EtOAc/isohexane). Yield – 31mgs (29%). NMR: 0.95 (m, 2H), 1.77 (m, 2H), 2.00 (m, 2H), 3.14 (m, 2H), 4.17 (m, 1H), 7.08 (m, 2H), 7.45 (m, 3H), 7.85 (m, 1H), 8.06 (m, 1H), 8.68 (m, 1H); m/z 313.

<u>Example 524</u>

<u>1-(4-Fluorobenzoyl)-4-(fur-2-ylcarbonyl)piperidine</u>

n-Butyl lithium (1.6M in hexanes – 1.23ml, 1.97mmol) was added dropwise under an inert atmosphere to a solution of furan (120µl, 1.64mmol) in THF (8ml) at 0°C (ice bath). The reaction mixture was allowed to warm to room temperature and stirred for 20min before re-cooling to 0°C. Magnesium bromide (363mg, 1.97mmol) was added to the reaction mixture followed by 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 120mg, 0.41mmol) in THF (1ml). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution (20ml) and then extracted with EtOAc (2x20ml). The organic phase was further washed with water (20ml) before drying ($MgSO_4$) and solvent removal *in vacuo*. The resulting yellow gum was triturated with Et_2O/Isohexane to yield a yellow solid (60mg, 49%). NMR (DMSO-d_6):

1.52 (m, 2H), 1.77 (m, 2H), 3.07 (m, 2H), 3.43 (m, 1H), 6.72 (m, 1H), 7.25 (m, 2H), 7.45 (m, 2H), 7.55 (m, 1H), 7.98 (m, 1H); m/z 302.

Example 525

1-(Fur-2-ylcarbonyl)-4-(3-methoxybenzoyl)piperidine

To a stirred solution of 4-(3-methoxybenzoyl)piperidine (Method 3; 52mg, 0.24mmol) and triethylamine (26mg, 0.26mmol) in DCM (3ml) was added 2-furoyl chloride (28mg, 0.21mmol). The reaction was stirred at room temperature for 1 hour then worked up. The reaction was transferred to a separating funnel then diluted to ~10ml with DCM. The DCM was then washed with 1M HCl (5ml), sat $NaHCO_3$ (5ml) and brine (5ml) then dried $MgSO_4$, filtered and evaporated to yield a solid (18mg, 24%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 3.25 (t, 2H), 3.75 (m, 1H), 3.90 (s, 3H), 4.30 (d, 2H), 6.60 (m, 1H), 6.90 (m, 1H), 7.20 (m, 1H), 7.50 (m, 2H), 7.60 (d, 1H), 7.75 (s, 1H); m/z 314.

Example 526

1-(4-Fluorobenzoyl)-4-[4-chloro-3-(hydroxymethyl)benzoyl]piperidine

To a stirred solution of 1-(4-fluorobenzoyl)-4-[4-chloro-3-(benzyloxymethyl)benzoyl] piperidine (Example 386; 50mg, 0.11mmols) in DCM at –78°C under Argon was added a 1M solution of BBr_3 in DCM (0.11ml, 0.11mmol). The reaction was stirred at –78°C for 10 minutes then allowed to warm 0°C and stirred for a further 20 minutes. The reaction was quenched with water (5ml) and extracted with DCM (2 x 5ml). The combined organics were washed with brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (10g Silica, 20 to 60% EtOAc/isohexane) to yield the product as a solid (21mg, 51%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.90 (m, 2H), 3.20 (m, 2H), 3.70 (m, 1H), 4.00 (br d, 2H), 4.70 (s, 2H), 5.20 (br s, 2H), 7.20 (t, 3H), 7.45 (m, 2H), 7.55 (d, 1H), 7.85 (m, 1H), 8.15 (m, 1H); m/z 376.

Example 527

1-(*t*-Butoxycarbonyl)-4-[4-(6-bromonaphth-2-ylthio)benzoyl]piperidine

60% Sodium hydride (717mg, 18mmol) was suspended in anhydrous dimethylformamide (50ml) under nitrogen at 5°C. To this was added portion-wise 6-bromo naphthalene-2-thiol (3.89g, 16mmol). The mixture was stirred at 5°C for 30 minutes. 1-(*t*-Butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine (Reference Example 12; 5.00g 16mmol) was

then added to the solution and the reaction heated at 60°C for 16 hours. The solution was poured into water (75ml) and washed with EtOAc (2x75ml). The organic phases were combined then washed with water then brine. The solution was dried over $MgSO_4$, after filtration and evaporation a solid was isolated. This was recrystallised from EtOAc/ isohexane resulting in a cream solid (2.96g, 35%). NMR (DMSO-d_6) 1.37 (s, 11H), 1.72 (m, 2H), 2.86 (m, 2H), 3.52 (m, 1H), 3.92 (m, 2H), 7.31 (d, 2H), 7.55 (d, 1H), 7.69 (d, 1H), 7.93 (m, 4H), 8.17 (s, 1H), 8.26 (s, 1H); m/z 470.

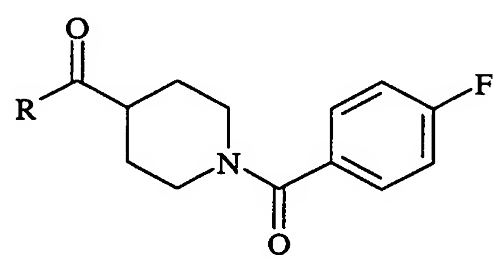
Example 528

1-(4-Fluorobenzoyl)-4-(thiazol-2-ylcarbonyl)piperidine

n-Butyl lithium (1.6M in hexanes – 275μl, 0.44mmol) was added dropwise under an inert atmosphere to a solution of thiazole (54.5mg, 0.4mmol) in THF (2ml) at -78°C. The reaction mixture was stirred at -78°C for 10min before 1-(4-fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl) piperidine (Method 2; 118mg, 0.4mmol) in THF (2ml) was added. The mixture was stirred at -78°C for 30min before being allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution (8ml) and then extracted with DCM (8ml). The biphasic mixture was passed through a phase separation cartridge and the solvent was removed *in vacuo*. The resulting residue was purified by chromatography (EtOAc/Isohexane gradient) to yield the product. (15mg, 12%). NMR: 1.2-2.2 (m, 6H), 3.10 (m, 2H), 3.90 (m, 1H), 7.12 (m, 2H), 7.43 (m, 2H), 7.71 (d, 1H), 8.03 (d, 1H); m/z 319.

Examples 529-534

The procedure described in Example 528 was repeated using the appropriate heterocycle to replace thiazole to give the compounds shown below.



Ex	R^1	NMR	M/z
529	4,5-Dimethylthiazol-2-yl		347
530	Benzothiazol-2-yl		369
531	5-Chlorobenzofuran-2-yl	1.90 (m, 6H), 3.17 (m, 2H), 3.50 (m, 1H), 7.12 (m, 2H), 7.48 (m, 5H), 7.70 (d, 1H)	386
532	Benzofuran-2-yl		352
533	5-Chlorobenzothien-2-yl	1.07 (m, 2H), 1.56 (m, 2H), 1.92 (m, 2H), 3.15 (m, 2H), 3.48 (m, 1H), 7.15 (m, 3H), 7.25 (m, 1H), 7.44 (m, 2H), 7.81 (d, 1H), 7.91 (dd, 1H)	402
534	Benzothien-2-yl	1.95 (m, 6H), 3.17 (m, 2H), 3.55 (m, 1H), 7.11 (m, 2H), 7.44 (m, 4H), 7.88 (m, 2H), 8.02 (s, 1H)	368

__Example 535__

1-(4-Fluorobenzoyl)-4-(5-cyanofur-2-ylcarbonyl)

The procedure described in Example 528 was repeated using 2-furonitrile instead of thiazole and lithium diisopropylamide (2M in THF/heptane) instead of n-butyl lithium. The product was isolated as a brown gum. NMR (DMSO-d6): 1.50 (m, 2H), 1.82 (m, 2H), 3.07 (m, 4H), 3.48 (m, 1H), 7.24 (m, 2H), 7.43 (m, 2H), 7.71 (d, 1H), 7.76 (d, 1H); m/z 327.

__Reference Example 11__

1-Benzyl-4-benzoylpiperidine

1,2-Dibromoethane (19µl, 0.22mmol) and a crystal of iodine were added to magnesium turnings (97mg, 4mmol) under an inert atmosphere. 1-Benzyl-4-bromopiperidine (1g, 4mmol) was added slowly as a solution in THF (8ml). Upon complete addition, the reaction mixture was heated at reflux for 10 minutes before cooling to room temperature. Benzonitrile (360µl, 3.5mmol) was added as a solution in THF (4ml) and the reaction mixture heated at reflux for 3 hours. After cooling, saturated ammonium chloride solution (15ml) was added, followed by EtOAc (15ml). The organic phase was further washed with water (15ml) and then dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue purified by chromatography (eluent: DCM/methanol/NH3 – 20/0.5/0.05) to yield the product as a brown gum (399mg, 41%). NMR (DMSO-d6): 1.60 (m, 2H), 1.75 (m,

2H), 2.100 (m, 2H), 2.84 (m, 2H), 3.37 (m, 1H), 3.48 (s, 2H), 7.27 (m, 5H), 7.50 (m, 2H), 7.61 (m, 1H), 7.94 (d, 2H); m/z 280.

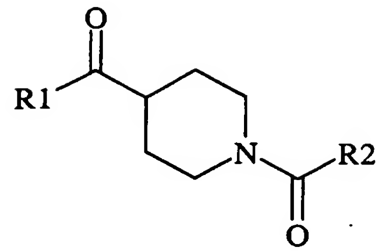
Example 536

1-Cyclopropylcarbonyl-4-(5-methylthien-2-yl)piperidine

1,2-Dibromoethane (35µl, 0.4mmol) and a crystal of iodine were added to magnesium turnings (228mg, 4mmol) under an inert atmosphere. 1-Benzyl-4-bromopiperidine (2g, 7.87mmol) was added slowly as a solution in THF (10ml). Upon complete addition, the reaction mixture was heated at reflux for 10 minutes before cooling to 0°C. 5-Methyl-2-thiophenecarboxaldehyde (15.74mmol) was added as a solution in THF (5ml) and the reaction mixture was warmed to room temperature and stirred for 16 hours. Saturated ammonium chloride solution (20ml) was added, followed by EtOAc (20ml). The organic phase was further washed with water (20ml) and then dried over magnesium sulphate. The solvent was removed under reduced pressure and the residual gum was dissolved in DCM (15ml) and stirred under argon. α-Chloroethyl chloroformate (826µl, 8mmol) was added to the solution and stirred at room temperature for 30min before concentrating *in vacuo*. The resulting residue was dissolved in methanol (10ml) and the solution heated at reflux for 40min before solvent removal. The product obtained was taken up in DCM (20ml), triethylamine (2.19ml, 15.74mmol) was added and the solution was split into 5 parts. One part of the solution (1.574mmol) was stirred under an inert atmosphere and cyclopropanecarbonyl chloride (1.574mmol) was added. The reaction mixture was stirred for 64 hours before quenching with saturated ammonium chloride solution (8ml) and addition of DCM (8ml). The biphasic mixture was passed through a phase separation cartridge and the solvent was removed *in vacuo*. The resulting residue was purified by chromatography (20% EtOAc/isohexane to 100% EtOAc gradient) to yield the product (49mg, 11%). NMR: 0.76 (m, 2H), 1.00 (m, 2H), 1.62 (m, 2H), 1.78 (m, 2H), 1.93 (m, 2H), 2.57 (s, 3H), 3.30 (m, 2H), 4.30 (m, 1H), 4.58 (m, 1H), 6.82 (d, 1H), 7.58 (d, 1H); m/z 278.

Example 537-550

The procedure described in Example 536 was repeated using the appropriate reagents to replace '5-Methyl-2-thiophenecarboxaldehyde' and 'cyclopropanecarbonyl chloride' to give the compounds shown below.



Ex	R1	R2	M/z
537	5-methylthien-2-yl	4-Trifluoromethoxyphenyl	398
538	3-Trifluorophenyl	4-Cyanophenyl	387
539	3-Trifluorophenyl	4-Trifluoromethoxyphenyl	446
540	3-Trifluorophenyl	4-Fluorophenyl	380
541	3-Trifluorophenyl	Cyclopropyl	326
542 [1]	3-Trifluorophenyl	Pyridin-2-yl	363
543 [2]	Thien-3-yl	4-Trifluoromethoxyphenyl	384
544	Thien-3-yl	4-Fluorophenyl	318
545	4-Chlorothien-2-yl	4-Fluorophenyl	352
546	4-Chlorothien-2-yl	4-Difluoromethoxyphenyl	400
547	4-Chlorothien-2-yl	Quinolin-2-yl	385
548	4,5-Dimethylfur-2-yl	4-Fluorophenyl	330
549	4,5-Dimethylfur-2-yl	Cyclohexyl	318
550	5-(Thien-2-yl)thien-2-yl	4-Difluoromethoxyphenyl	448

[1] Method used corresponding carboxylic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride instead of corresponding acid chloride.

[2] NMR: 1.60-2.00 (m, 6H), 3.12 (m, 2H), 3.37 (m, 1H), 7.28 (m, 2H), 7.38 (m, 1H), 7.49 (m, 2H), 7.59 (m, 1H), 8.09 (m, 1H).

Reference Example 12

1-(*t*-Butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine

4-(4-Fluorobenzoyl)piperidine p-toluenesulfonate (20.00g, 53mmol) was dissolved in DCM (200ml) and triethylamine (14.68ml, 106mmol). To this was added dropwise a solution of di-tert-butyl dicarbonate (12.65g, 58mmol) in DCM (100ml). The mixture was stirred at ambient temperature for 3 hours. The solution was then washed with water (100ml) then saturated $NaHCO_3$. The solution was then dried over $MgSO_4$, after filtration and evaporation

an oil was isolated. This was chromatographed on silica eluting with 0-20% EtOAc/ isohexane. The relevant fractions were combined to afford a white solid (14.22g, 88%). NMR (DMSO-d_6) 1.38 (s, 11H), 1.72 (m, 2H), 2.89 (m, 2H), 3.60 (m, 1H), 3.95 (m, 2H), 7.32 (t, 2H), 8.05 (m, 2H); m/z 308.

Example 551

1-(Cyclopentylcarbonyl)-4-(4-chorobenzoyl)-4-ethylpiperidine

The title compound was prepared using the same procedure as was used for Examples 130-345 and Reference Examples 3-5 above. The method type was "XXe". M/z 364.4.

Example 552

1-(4-Fluorobenzoyl)-4-(3-cyanobenzoyl)piperidine

1-(4-Fluorobenzoyl)-4-ethoxycarbonyl-4-(3-cyanobenzoyl)piperidine (Method 13) was split into two portions of 0.19 mmol and heated with lithium chloride (0.37 mmol) and water (several drops) in dimethyl acetamide (2ml) in the microwave at 200°C for 10-15 minutes. The reaction mixture was concentrated *in vacuo*, the residue partitioned between water and DCM and passed through a phase separation cartridge, the crude material was purified on a Biotage Quad3+ flash chromatography system eluting with 25% EtOAc/isohexane to furnish the title compound. NMR: 8.21 (1H, s), 8.19 (1H, d), 7.87 (1H, d), 7.65 (1H, dd), 7.43 (2H, dd), 7.12 (2H, dd), 3.53 (1H, m), 3.19 (2H, bs), 2.0-1.71 (4H, m), 1.30 (1H, m); m/z 332.5.

Example 553

1-(2-Methyl-4,5,6,7-tetrahydrobenzofuran-3-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine

The title compound was prepared using the same procedure as was used for Examples 130-345 and Reference Examples 3-5 above. The method type was "YYb". M/z 370.

Example 554

1-(Pyrrolidin-1-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine

To a solution of pyrrolidine (81μl, 1.0mmol) and DIEA (174μl, 1.0mmol) in DCM (5ml) was added a pre-prepared solution of 4-(4-fluorobenzoylpiperidine) hydrochloride (293mg, 1.2mmol) and triphosgene (297mg, 1.0mmol) in DCM (5ml). Following completion of the addition DIEA (2.0mmol) was added to the reaction mixture and stirred for 16 hours at

room temperature. After this time, further triphosgene (1.0mmol), pyrrolidine (1.0mmol) and DIEA (1.0mmol) were added to the reaction mixture to encourage reaction to completion. After stirring at room temperature for a further 24 hours the reaction had reached completion and was worked up. Reaction mixture was transferred to a separating funnel and diluted to approximately 5ml with DCM. The DCM was washed with 2M HCl (10ml), water (10ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield the crude product as a yellow oil. Purification by prep LCMS yielded the product as a yellow solid (85mg, 0.28mmol, 28%). NMR (DMSO-d_6): 1.48 (q, 2H), 1.71 (br s, 6H), 2.84 (t, 2H), 3.23 (t, 5H), 3.55 (dt, 1H), 3.63 (br d, 2H), 7.34 (t, 2H), 8.06 (dd, 2H); m/z 305.

Example 555

1-(*t*-Butoxycarbonyl)-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine

1-(*t*-Butoxycarbonyl)-4-[4-(6-bromonaphth-2-ylthio)benzoyl]piperidine (Example 527; 2.93g, 5.6mmol) was dissolved in DCM (50ml), to this was added 3-chloroperoxybenzoic acid (5.79g, 17mmol). The reaction was stirred for 18 hours before washing with 2M NaOH (25ml), drying ($MgSO_4$) before evaporation to give crude material. The compound was purified by chromatography on silica gel eluting with 0-10% EtOAc in toluene. The title compound was obtained as a white solid (958mg, 31%). NMR (DMSO-d_6) 1.31 (m, 11H), 1.71 (m, 2H), 2.86 (m, 2H), 3.59 (m, 1H), 3.89 (m, 2H), 7.83 (d, 1H), 7.97 (d, 1H), 8.14 (m, 6H), 8.34 (s, 1H), 8.79 (s, 1H); m/z 559.

Example 556

4-[4-(6-Bromonaphth-2-ylsulphonyl)benzoyl]piperidine hydrochloride

1-(*t*-Butoxycarbonyl)-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine (Example 555; 944mg, 1.7mmol) was dissolved in EtOAc (25ml) then treated with 4M HCl in EtOAc then stirred for 3 hours. The slurry was then evaporated then slurried in ether (40ml) before filtration to give the title compound as a white solid (744mg, 89%). NMR (DMSO-d_6) 1.80 (m, 4H), 2.97 (m, 2H), 3.26 (m, 2H), 3.74 (m, 1H), 7.83 (d, 1H), 7.97 (d, 1H), 8.14 (m, 6H), 8.34 (s, 1H), 8.79 (m, 2H), 9.04 (bs, 1H); m/z 458.

Example 557

1-[2-(*t*-Butoxycarbonylamino)acetyl]-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine

4-[4-(6-Bromonaphth-2-ylsulphonyl)benzoyl]piperidine hydrochloride (Example 556; 200mg, 0.41mmol) was added to a solution of N-(tert-butoxycarbonyl)glycine (78mg, 0.45mmol), 1-hydroxybenzotriazole monohydrate (68mg, 0.45mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86mg, 0.45mmol) and 4-methylmorpholine (0.093ml, 0.85mmol) in N,N-dimethylformamide (20ml). The mixture was stirred at ambient temperature for 16 hours. The volatiles were removed by evaporation and the residue was dissolved in DCM (20ml) and water (10ml), the layers were separated before washing with 2M HCl then saturated $NaHCO_3$. Evaporation afforded a white solid. The compound was purified by chromatography on silica gel eluting with 0-2% methanol in DCM. The title compound was obtained as a white solid (198mg, 80%). NMR (DMSO-d_6) 1.40 (m, 11H), 1.77 (m, 2H), 2.74 (m, 2H), 3.11 (m, 1H), 3.71 (m, 4H), 4.27 (m, 1H), 6.66 (m, 1H), 7.83 (d, 1H), 7.97 (d, 1H), 8.14 (m, 6H), 8.34 (s, 1H), 8.79 (s, 1H); m/z 615.

Example 558

1-(2-Aminoacetyl)-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine hydrochloride

The title compound was prepared from 1-[2-(*t*-butoxycarbonylamino)acetyl]-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine (Example 557) by a the procedure of Example 556. NMR (DMSO-d_6) 1.43 (m, 2H), 1.80 (m, 2H), 2.84 (m, 1H), 3.17 (m, 1H), 3.80 (m, 4H), 4.31 (m, 1H), 7.83 (d, 1H), 7.97 (d, 1H), 8.14 (m, 6H), 8.34 (s, 1H), 8.79 (s, 1H); m/z 515.

Example 559

1-(Imino(phenyl)methyl)-4-[4-(6-bromonaphth-2-ylsulphonyl)benzoyl]piperidine dihydrochloride

4-[4-(6-Bromonaphth-2-ylsulphonyl)benzoyl]piperidine hydrochloride (Example 556; 150mg, 0.30mmol), methyl benzimidate hydrochloride (104mg, 0.61mmol) and triethylamine (0.17ml, 1.2mmol) were dissolved in methanol/ chloroform (20ml) and stirred for 16 hours. Methyl benzimidate hydrochloride (104mg, 0.61mmol) and triethylamine (0.17ml, 1.2mmol) were further added followed by stirring for 16 hours. The solvent was evaporated before the compound was purified by chromatography on silica gel eluting with 0-15% ethanol in DCM. The compound was purified further on a reverse phase bond elute. The title compound was

obtained as a white solid (90mg, 47%). NMR, DMSO-d_6 1.80 (m, 4H), 3.33 (m, 4H), 3.84 (m, 1H), 7.61 (m, 5H), 7.83 (d, 1H), 7.97 (d, 1H), 8.14 (m, 6H), 8.34 (s, 1H), 8.79 (s, 1H); m/z 561.

Preparation of Starting Materials

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

1-(4-Fluorobenzoyl)-4-(ethoxycarbonyl)piperidine

To a stirred solution of ethylisonipecotate (2.5g, 0.016mol) and triethylamine (1.77g, 0.017mol) in DCM (100ml) was added 4-flurobenzoyl chloride (2.39g, 0.015mol). The reaction was stirred at room temperature for one hour then worked up. The reaction was transferred to a separating funnel and diluted to ~150ml with DCM. The DCM was washed with 1M HCl (100ml), sat $NaHCO_3$ (100ml)and brine (50ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil (3.67g, 83%). NMR (DMSO-d_6): 1.20 (t, 3H), 1.60 (m, 2H), 1.90 (m, 2H), 2.65 (m, 1H), 3.10 (m, 2H), 3.95 (br d, 2H), 4.10 (q, 2H), 7.25 (t, 2H), 7.55 (m, 2H); m/z 280.

Method 2

1-(4-Fluorobenzoyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of 1-(4-fluorobenzoyl)-4-(ethoxycarbonyl)piperidine (Method 1; 1g, 3.58mmol) in anhydrous THF (30ml) was added N,O-dimethylhydroxylamine hydrochloride (350mg, 3.58mmol). The resulting solution was cooled to –10°C before the addition of a 2M solution of isopropyl magnesium chloride (3.58ml, 7.16mmol). The reaction was stirred at –10°C for 15 minutes then allowed to warm to room temperature. The reaction was stirred at room temperature for 60 minutes before the addition of further isopropyl magnesium chloride (0.18ml, 0.36mmol). The reaction was then stirred for a further 10 minutes before working up. The reaction was quenched with sat NH_4Cl solution (~20ml) then extracted with EtOAc (2 x 20ml). The combined organic layers were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield the title compound (880mg, 84%). NMR

(DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 3.00 (m, 1H), 3.10 (m, 2H), 3.15 (s, 3H), 3.70 (s, 3H), 4.05 (m, 2H), 7.20 (t, 2H), 7.45 (m, 2H); m/z 295.

Method 3

4-(3-Methoxybenzoyl)piperidine

To a stirred 1M solution of 3-methoxyphenyl magnesium bromide in THF (12ml, 0.012mols) was added a solution of 1-acetylpiperidine-4-carbonitrile (1g, 6.57mols) in THF (4ml). The reaction was then left to stir overnight in the dark. The reaction was quenched with sat NH_4Cl and then warmed to 40°C and stirred at this temperature for 1 hour. The volatile organics were removed under reduced pressure and the resulting aqueous layer was extracted with ether (2 x 20ml). The organic layers were combined, washed with brine then evaporated to yield an oil. This oil was dissolved in dioxane (7ml) and treated with 5M HCl (7ml). The reaction was heated to 100° and stirred at this temperature overnight. The reaction was the cooled to room temperature and evaporated under reduced pressure. The resulting crude material was dissolved in DCM and washed with 2M NaOH, water and brine. The solvent was evaporated under reduced pressure to yield a yellow oil. This oil was dissolved in a small amount of MeOH and loaded onto an SCX-2 column. The column was eluted with MeOH until no further impurities eluted off. The desired product was then eluted with 1% NH_3/MeOH to yield an oil (52mg, 4%). m/z 220.

Method 4

3-Methyl-4-(4-fluorobenzoyl)piperidine hydrochloride

To a stirred solution of 1-(t-butoxycarbonyl)-3-methyl-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine (Method 5; 85mg, 0.3mmol) in anhydrous THF (2ml) at 0°C was added a 1M solution of 4-fluorophenyl magnesium bromide in THF (1ml, 1mmol). The reaction was stirred at 0°C for 1 hour then allowed to warm to room temperature and stirred for a further 90 minutes. At this stage further 4-fluorophenyl magnesium bromide (0.5ml, 0.5mmol) was added and the reaction was stirred for a further hour. The reaction was quenched with sat NH_4Cl solution (~5ml) then extracted with EtOAc (2 x 5ml). The combined organic layers were then washed with brine (~5ml), dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was dissolved in DCM (~1ml) and treated with TFA (~0.1ml) then left to stir overnight at room temperature. The reaction mixture was then transferred to a separating funnel and diluted to ~5ml with DCM. The DCM layer was then

washed with 1M NaOH and evaporated to yield an oil. This oil was eluted through an Isolute SCX-2 column using MeOH. When all impurities had eluted off the product was eluted with 1% NH_3/MeOH. This product was dissolved in ether then treated with 1.1eq of 1M HCl in ether. The resulting suspension was evaporated under reduced pressure to yield a solid. This solid was left under high vac overnight to yield the product as the hydrochloride salt (22mg, 30%). NMR (DMSO-d_6): 0.90 (d, 3H), 1.90 (m, 1H), 2.00 (m, 2H), 2.40 (m, 1H), 3.20 (m, 3H), 3.90 (m, 1H), 7.30 (t, 2H), 8.05 (m, 2H), 8.60 (br s, 2H); m/z 222.

Method 5

1-(*t*-Butoxycarbonyl)-3-methyl-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of N-Boc-3-methyl-4-piperidine carboxylic acid (100mg, 0.41mmol), N,O-dimethyl hydroxylamine hydrochloride (40mg, 0.41mmol) and N-methyl morpholine (41mg, 0.41mmol) in DCM (5ml) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (79mg, 0.41mmol). The resulting solution was stirred at room temperature for 48 hours. The reaction mixture was transferred to a separating funnel and washed with 1M HCl (2 x 5ml), sat $NaHCO_3$ (5ml) and brine (5ml) then dried ($MgSO_4$), filtered and evaporated to yield a solid (85mg, 73%). NMR (DMSO-d_6): 0.85 (d, 3H), 1.45 (s, 9H), 1.47 (m, 1H), 1.80 (m, 1H), 2.10 (m, 1H), 3.05 (m, 3H), 3.10 (s, 3H), 3.20 (m, 1H), 3.65 (m, 1H), 3.70 (s, 3H), 3.80 (m, 1H).

Method 6

1-(4-Fluorophenylsulphonyl)-4-(ethoxycarbonyl)piperidine

To a stirred solution of ethylisonipecotate (15g, 0.095mol) and triethylamine (10.6g, 0.105mol) in DCM (380ml) at 0°C was added a solution of 4-fluorobenzenesulfonylchloride (17.6g, 0.09mol) in DCM (20ml). The reaction was stirred at 0°C for 10 minutes then allowed to warm to room temperature and stirred for a further 2 hours. The reaction mixture was transferred to a separating funnel and washed with 2M HCl (80ml), water (40ml), sat $NaHCO_3$ (40ml) and brine (40ml) and then dried ($MgSO_4$), filtered and evaporated to yield a white solid (25.75g, 88%). NMR (DMSO-d_6): 1.15 (t, 3H), 1.55 (m, 2H), 1.85 (m, 2H), 2.35 (m, 1H), 2.45 (m, 2H), 3.50 (m, 2H), 4.05 (q, 2H), 7.45 (t, 2H), 7.80 (m, 2H); m/z 316.

Method 7

1-(Isopropylsulphonyl)-4-(ethoxycarbonyl)piperidine

The title compound was prepared by the procedure of Method 6. NMR (DMSO-d_6): 1.20 (m, 9H), 1.50 (m, 2H), 1.85 (m, 2H), 2.55 (m, 1H), 2.85 (m, 2H), 3.30 (m, 1H), 3.60 (m, 2H), 4.10 (q, 2H); m/z 264.

Method 8

1-(4-Fluorophenylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

To a stirred solution of 1-(4-fluorophenylsulphonyl)-4-(ethoxycarbonyl)piperidine Method 6; 8g, 0.025mol) and N,O-dimethyl hydroxylamine hydrochloride (2.49g, 0.025mol) in anhydrous THF (200ml) at 0°C was added a 2M solution of iso propyl magnesium chloride in THF (26ml, 0.053mol). The reaction was stirred at 0°C for ten minutes then allowed to warm to room temperature and left to stir for two and a half hours. The reaction was quenched with sat NH_4Cl solution (100ml) and extracted with EtOAc (2x100ml). The combined organic phases were washed with brine then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (50g Silica, 20% EtOAc/isohexane to 60% EtOAc/isohexane) to yield an oil which crystallised on standing (6g, 73%). NMR (DMSO-d_6): 1.60 (m, 2H), 1.80 (m, 2H), 2.55 (m, 2H), 2.70 (m, 1H), 3.05 (s, 3H), 3.65 (m, 5H), 7.40 (t, 2H), 7.80 (m, 2H); m/z 331.

Method 9

1-(Isopropylsulphonyl)-4-(*N*-methyl-*N*-methoxycarbamoyl)piperidine

The title compound was prepared by the procedure of Method 8, except the product did not require chromatography. NMR (DMSO-d_6): 1.20 (d, 6H), 1.50 (m, 2H), 1.75 (m, 2H), 2.85 (m, 1H), 2.95 (m, 2H), 3.10 (s, 3H), 3.30 (m, 1H), 3.70 (s, 3H); m/z 279.

Method 10

5-Bromo-2-chloro-1-(benzyloxymethyl)phenyl

To a stirred solution of 5-bromo-2-chloro benzyl alcohol (2.5g, 0.011mols) in DMF (100ml) was added NaH (60% suspension) (497mg, 0.012mols). The resulting reaction was stirred at room temperature for 30 minutes before the addition of benzyl bromide (1.79g, 0.01mols). The reaction was stirred at room temperature for 3 hours then quenched with sat NH_4Cl solution (10ml). The volatiles were removed under reduced pressure and the resulting

slurry was partitioned between EtOAc and water (~100ml of each). The layers were separated and the aqueous was re-extracted with EtOAc (~30ml). The organic layers were combined, washed with brine (30ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (20g Silica, isohexane to 10% EtOAc/isohexane) to yield the product as an oil (1.32g, 42%). NMR (DMSO-d_6): 4.58 (s, 2H), 4.60 (s, 2H), 7.30 (m, 1H), 7.35 (m, 4H), 7.40 (s, 1H), 7.50 (m, 1H), 7.65 (m, 1H); m/z 310.

Method 11

5-Bromo-2-chloro-1-(methoxymethyl)phenyl

To a stirred solution of 5-Bromo-2-Chloro-benzyl alcohol (5.46g, 0.025mols) in anhydrous THF (50ml) was added NaH (60% suspension) (1.18g, 0.03mols). The resultant reaction was stirred at room temperature for 20 minutes before the addition of methyl iodide (4.68g, 0.033mols). The reaction was left to stir for 3 hours then quenched with 2M HCl (~20ml) and extracted with EtOAc (2 x 15ml). The combined organic layers were washed with brine (20ml) then dried ($MgSO_4$), filtered and evaporated to yield an oil. This oil was purified by column chromatography (50g Silica, 20% EtOAc/isohexane) to yield a colourless oil (5.46g, 93%). NMR (DMSO-d_6): 3.35 (s, 3H), 4.45 (s, 2H), 7.40 (d, 1H), 7.50 (m, 1H), 1.60 (m, 1H); m/z: 234.

Method 12

1-(4-Fluorobenzoyl)-4-ethoxycarbonylpiperidine

To a solution of ethyl isonipecotate (95 mmol) and triethylamine (114 mmol) in DCM (350 ml) at 5°C was added 4-fluorobenzoyl chloride (90 mmol). The resultant suspension was allowed to stir at this temperature for 3 hours. The reaction mixture was then washed with 1M HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and the filtrate concentrated *in vacuo* to afford the title compound. M/z: 280.5.

Method 13

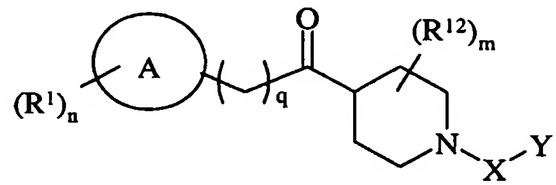
1-(4-Fluorobenzoyl)-4-ethoxycarbonyl-4-(3-cyanobenzoyl)piperidine

A solution of 1-(4-fluorobenzoyl)-4-ethoxycarbonylpiperidine (Method 12; 1.2 mmol) in THF (10 ml) was added to LHMDS (3 mmol) at room temperature and under argon, 3-cyanobenzoyl chloride (4.8 mmol) was then added and the reaction allowed to stir at room temperature over night. The reaction mixture was quenched with water, concentrated *in*

vacuo, and the residue partitioned between water and DCM before being passed through a phase separation cartridge. The crude product was purified on a Biotage Quad3+ flash chromatography system, eluting with 25% EtOAc/isohexane to give the title compound. M/z: 409.2.

__Claims__

1. The use of a compound of formula (I):



(I)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O-, -C(=NR^{11})- or -CH$_2$-; wherein $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-4}alkyl, carbocyclyl and heterocyclyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl,

N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-N-(C_{1-4}alkyl)amino, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, N-(C_{1-4}alkyl)aminothiocarbonylthio, N,N-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-N-(C_{1-4}alkyl)amino, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^4, **R^5**, **R^7** **R^9** and R^{13} are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1;

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

2. The use of a compound of formula (I) as claimed in claim 1 wherein Ring A is phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl, furyl, thiazolyl, 1,3-benzothiazolyl, benzofuryl or benzothienyl; or a pharmaceutically acceptable salt thereof.

3. The use of a compound of formula (I) as claimed in any one of claims 1-2 wherein R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein

R^3 is selected from halo, hydroxy, C_{1-4}alkoxy, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; and

Z is -S(O)$_a$- or -O-; wherein a is 0 to 2;

or a pharmaceutically acceptable salt thereof.

4. The use of a compound of formula (I) as claimed in any one of claims 1-3 wherein n is 0-3; wherein the values of R^1 may be the same or different; or a pharmaceutically acceptable salt thereof.

5. The use of a compound of formula (I) as claimed in any one of claims 1-4 X is -C(O)-; or a pharmaceutically acceptable salt thereof.

6. The use of a compound of formula (I) as claimed in any one of claims 1-5 wherein Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino,

N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, carbocyclyl, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl, C_{1-4}alkanoyl and C_{1-4}alkoxycarbonyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen; and

R^8 is selected from halo;

or a pharmaceutically acceptable salt thereof.

7. The use of a compound of formula **(I)** as claimed in any one of claims 1-6 wherein R^{12} is 4-methyl, 4-ethyl, 4-propyl or 3-methyl; or a pharmaceutically acceptable salt thereof.

8. The use of a compound of formula **(I)** as claimed in any one of claims 1-7 wherein q is 0; or a pharmaceutically acceptable salt thereof.

9. The use of a compound of formula **(I)** as depicted in claim 1 wherein:

Ring A is phenyl, 1,3-benzodioxolyl, thienyl, cyclopentyl, pyridyl, furyl, thiazolyl, 1,3-benzothiazolyl, benzofuryl or benzothienyl;

R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, carbocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; wherein

R^3 is selected from halo, hydroxy, C_{1-4}alkoxy, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; and

Z is -S(O)$_a$- or -O-; wherein a is 0 to 2;

X is a direct bond, -C(O)-, -S(O)$_2$-, -C(O)NR^{11}-, -C(S)NR^{11}-, -C(O)O-, -C(=NR^{11})- or -CH$_2$-; wherein R^{11} is selected from hydrogen, C_{1-4}alkyl, carbocyclyl and heterocyclyl;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5; wherein

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^6 is selected from halo, nitro, cyano, trifluoromethyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonylamino, carbocyclyl, heterocyclyl and carbocyclylC_{0-4}alkylene-Z-; wherein R^6 may be optionally substituted on carbon by one or more R^8;

R^5 is selected from C_{1-4}alkyl, C_{1-4}alkanoyl and C_{1-4}alkoxycarbonyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)- or -OC(O)NR^{10}-; wherein a is 0 to 2; wherein R^{10} is selected from hydrogen; and

R^8 is selected from halo;

R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1; and

q is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

10. A compound of formula **(I)** as claimed in any one of claims 1-9 selected from:

1-(3-fluoro-4-methoxybenzoyl)-4-(4-fluorobenzoyl)piperidine;

1-(quinoline-3-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;

1-(quinoline-2-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine;

1-(5-trifluoromethylfur-2-yl)-4-(4-fluorobenzoyl)piperidine;

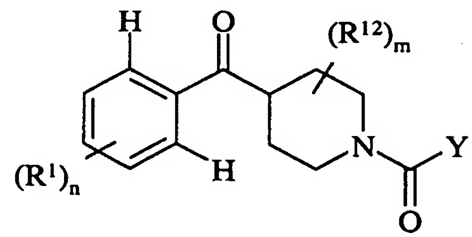
1-(3-trifluoromethoxybenzoyl)-4-(4-fluorobenzoyl)piperidine;

1-(tetrahydrofur-2-ylcarbonyl)-4-(4-chlorobenzoyl)piperidine;

1-(5-trifluoromethylfur-2-yl)-4-(4-chlorobenzoyl)piperidine;

1-(pyrid-2-ylcarbonyl)-4-(4-chlorobenzoyl)piperidine;
1-(thiazol-4-ylcarbonyl)-4-(4-chlorobenzoyl)piperidine;
1-(3,3,3-trifluoropropionyl)-4-(4-fluorobenzoyl)piperidine;
1-(4-fluorobenzoyl)-4-(3-mesylbenzoyl)piperidine;
or a pharmaceutically acceptable salt thereof.

11. A compound of formula **(Ig)**:



(Ig)

wherein:

R^1 is a substituent on carbon and is selected from halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylS(O)$_2$, *N*-(C_{1-4}alkyl)sulphamoyl or *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3;

n is 0-3; wherein the values of R^1 may be the same or different;

Y is phenyl, pyrimidine, furan, thiophene or thiazole; wherein Y may be optionally substituted on carbon by one or more R^2;

R^2 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, *N*-(C_{1-4}alkyl)aminothiocarbonylthio or *N,N*-(C_{1-4}alkyl)$_2$aminothiocarbonylthio; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl,

N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl or C_{1-4}alkylsulphonylamino; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

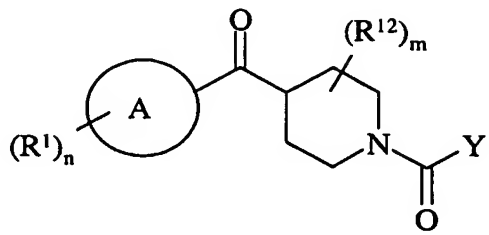
R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not 1,4-dibenzoylpiperidine; 4-hydroxy-1,4-dibenzoylpiperidine; 1-(3,4,5-trimethoxybenzoyl)-1-benzoylpiperidine; 1,4-di-(4-methylbenzoyl)piperidine; 1-(4-chlorobenzoyl)-4-benzoylpiperidine; 1-(3-nitrobenzoyl)-4-benzoylpiperidine; 1-(2-methoxy-4,6-ditrifluoromethylbenzoyl)-4-(4-chlorobenzoyl)piperidine; 1-(2,6-difluorobenzoyl)-4-benzoylpiperidine; 1-(3-trifluoromethylbenzoyl)-4-(benzoyl)piperidine; 1-(4-aminobenzoyl)-4-(4-fluorobenzoyl)piperidine; 1-(2-chloro-4-nitrobenzoyl)-4-benzoylpiperidine; 1-(4-methoxybenzoyl)-4-benzoylpiperidine; 1-(4-*t*-butylbenzoyl)-4-benzoylpiperidine; 1-(2,4-dihydroxybenzoyl)-4-(4-fluorobenzoyl)piperidine; 1-(4-nitrobenzoyl)-4-(4-fluorobenzoyl)piperidine; 1-(pyrid-3-ylcarbonyl)-4-(4-fluorobenzoyl)piperidine; 1-(thien-2-ylcarbonyl)-4-benzoylpiperidine; 1-(thien-2-ylcarbonyl)-4-(4-methylbenzoyl)piperidine; or 1-(fur-2-ylcarbonyl)-4-benzoylpiperidine.

12. The use of a compound of formula **(Ih)**:



(Ih)

wherein:

Ring A is selected from carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

$\mathbf{R^1}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^1 may be optionally substituted on carbon by one or more groups selected from R^3; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^4;

n is 0-5; wherein the values of R^1 may be the same or different;

Y is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or heterocyclyl; wherein Y may be optionally substituted on carbon by one or more R^2; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^5;

$\mathbf{R^2}$ is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-*N*-(C_{1-4}alkyl)amino, *N*-(C_{1-4}alkyl)sulphamoyl,

N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, aminothiocarbonylthio, N-(C_{1-4}alkyl)aminothiocarbonylthio, N,N-(C_{1-4}alkyl)$_2$aminothiocarbonylthio, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^2 may be optionally substituted on carbon by one or more groups selected from R^6; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7;

R^3 and **R^6** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, C_{1-4}alkoxycarbonyl-N-(C_{1-4}alkyl)amino, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{0-4}alkylene-Z- and heterocyclylC_{0-4}alkylene-Z-; wherein R^3 and R^6 may be independently optionally substituted on carbon by one or more R^8; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^4, **R^5**, **R^7** **R^9** and R^{13} are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^8 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl;

Z is -S(O)$_a$-, -O-, -NR^{10}-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -OC(O)NR^{10}- or -SO$_2$NR^{10}-; wherein **a** is 0 to 2; wherein **R^{10}** is selected from hydrogen and C_{1-4}alkyl;

R^{12} is hydroxy, methyl, ethyl or propyl;

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11βHSD1.

13. A pharmaceutical composition which comprises a compound of formula **(I)** or **(Ig)**, or a pharmaceutically acceptable salt thereof, as claimed in claims 10 or 11, in association with a pharmaceutically-acceptable diluent or carrier.

14. A compound of the formula **(I)** or **(Ig)**, or a pharmaceutically acceptable salt thereof, as claimed in claims 10 or 11, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

15. A compound of the formula **(I)** or **(Ig)**, or a pharmaceutically acceptable salt thereof, as claimed in claims 10 or 11, for use as a medicament.

16. The use of a compound of the formula **(I)** or **(Ig)**, or a pharmaceutically acceptable salt thereof, as claimed in claims 10 or 11, in the manufacture of a medicament for use in the production of an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man.

17. The use as claimed in any one of claims 1-9, 12 and 16 wherein production of, or producing an, 11βHSD1 inhibitory effect refers to the treatment of metabolic syndrome.

18. The use as claimed in any one of claims 1-9, 12 and 16 wherein production of, or producing an, 11βHSD1 inhibitory effect refers to the treatment of diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly diabetes and obesity.

19. The use as claimed in any one of claims 1-9, 12 and 16 wherein production of, or producing an, 11βHSD1 inhibitory effect refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

20. A method of producing an 11βHSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, as claimed in any one of claims 1-10, or a compound

of formula **(Ig)** as claimed in claim 11, or a compound of formula **(Ih)** as claimed in claim 12, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PC[redacted] 03/04318

A. CLASSIFICATION OF SUBJECT MAT[redacted]
IPC 7 C07D211/32 C07D401/06 C07D405/06 C07D417/06 A61K31/443
A61K31/444 A61K31/445 A61K31/4427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 10 287671 A (NIPPON SODA CO LTD) 27 October 1998 (1998-10-27) see general formula and activity ---	1-9, 12-20
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2004	27/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT[redacted]03/04318

C.(Continuation) DOCUMENTS CONSIDE[redacted]O BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JP 60 226877 A (FUJISAWA YAKUHIN KOGYO KK) 12 November 1985 (1985-11-12) the whole document ---	1-9, 12-20
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A	WO 01 90091 A (BARF TJEERD ;BIOVITRUM AB (SE); KURZ GUIDO (SE); VALLGAARDA JERK () 29 November 2001 (2001-11-29) the whole document -----	1-20

International application No.
PCT/GB 03/04318

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-10,12-20(all partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,12-20(all partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty, particularly due to the claims 13-15, which are first medical use claims of the compounds of claim 1, and due to the definitions in formula I of A,X and Y, with the cascading substitution patterns of R1,R3,R2 and R6. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds of claims 10 and 11, and the use of the compounds of claim 12 for the diseases stated in claims 17-19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT 03/04318

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INTERNATIONAL SEARCH REPORT

International [redacted] Application No
PCT/[illegible] 03/04318

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			US	2003176476	A1	18-09-2003
			US	2003199501	A1	23-10-2003
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